Review of the clinical practice literature on allogeneic red blood cell transfusion

Special Supplement

Supplément spécial

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Abstract

Objective: To review the evidence describing practice variation in the transfusion of allogeneic red blood cells as well as the risks, benefits, harms and costs associated with anemia and transfusion.

Literature search and selection: Searches of MEDLINE from January 1966 to December 1996 were combined with manual searches of bibliographies and references from experts. Two reviewers examined the abstracts of citations to identify those related to clinical practice involving red blood cell transfusions. Disagreement was resolved through consensus.

Literature synthesis: Selected articles were classified by study design and topic. Inferences were derived from the evidence.

Results: Of the 189 articles reviewed, 78 (41%) were interventional and 111 (59%) were observational studies. A number of observational studies reported a decrease in the number of transfusions since the mid 1980s, significant practice variation among physicians, institutions and various medical and surgical settings and rates of 4% to 66% of unnecessary transfusion. Of the 47 randomized clinical trials (RCTs) we found, 6 evaluated various "transfusion thresholds." Only 1 of the 6 RCTs in patients with sickle-cell disease was considered level I evidence. There was no consensus on a hemoglobin concentration that would act as a transfusion threshold. Two cohort studies suggested that adverse outcomes from anemia are greatest in patients with cardiac disease. In 8 studies evaluating the effect of hemoglobin concentration on health-related quality of life and symptoms such as dyspnea, fatigue and exercise capacity, no correlations or associations were noted.

Conclusion: The rate of transfusion has decreased since 1985; practice varies significantly as does the rate of unnecessary transfusion. Education programs and the use of algorithms may increase the appropriateness of RBC use. There was insufficient evidence to justify setting an optimal hemoglobin concentration as a transfusion threshold following acute or chronic anemia. RCTs should be conducted to determine best transfusion practice in a variety of clinical settings. Prospective cohort studies are also needed to describe transfusion practice.

Allogeneic red blood cell (RBC) transfusions have been an important measure in the clinical care of many patients. They have been recommended for increasing oxygen delivery as well as for alleviating the symptoms of anemia.[1–5] In the 1940s and early 1950s, allogeneic RBC transfusions were ordered readily as practitioners believed transfusion-related risks to be negligible. As early as the late 1950s, a more cautious approach was being suggested,[6,7] but many practitioners continued to use transfusions with little overt concern about the risks.[7] The appearance of viruses in the blood system, including the human immunodeficiency virus (HIV) and several types of viruses causing hepatitis, as well as the decreasing availability of blood, resulted in recommendations for a more conservative use of allogeneic RBCs.[2–4,8–15]

Despite increasing interest in all aspects of transfusion practice, we were un-

able to identify any systematic reviews of clinical practice in this area. To help health care practitioners make decisions about transfusion, we thought it important to describe transfusion practice by addressing the following questions: What are the indications for allogeneic RBC transfusions? Have there been changes in clinical transfusion practice and utilization of RBCs over time? Which patients are most frequently transfused with allogeneic RBCs? Is there published evidence of significant practice variation and unnecessary use of RBCs?

We also questioned the therapeutic aspects of this intervention: What are the benefits, risks, harms and costs associated with anemia and allogeneic RBC transfusions? What patient characteristics or diseases increase the risk of adverse outcomes following anemia? This systematic evaluation is an attempt to answer these questions and to provide a synthesis of a vast literature for physicians making transfusion-related clinical decisions.

Methods

Literature search and selection

A search of Medline from January 1966 to July 1996 was constructed using the following medical subject headings (MeSHs): blood transfusion, erythrocyte transfusion and blood component transfusion. This was combined with other searches using the MeSHs blood transfusion, adverse effects, postoperative complications, aged, immunosuppression and infection. The searches were designed to find these words in titles and abstracts of citations in all languages and study designs. In addition, manual searches of bibliographies were carried out. In this review, we excluded all laboratory studies and human studies focusing on physiologic mechanisms. Foreign language articles without a French or English abstract were also excluded.

The MEDLINE citation lists were scanned by 2 reviewers (PH,LC). Preliminary selection consisted of determining if a citation involved transfusion practice in humans. The abstracts of selected citations were then reviewed by the same 2 people to ensure that the following criteria defining clinical RBC transfusion practice were met: original data were used (i.e., primary studies); studies were in humans; clinical aspects of allogeneic RBC transfusions were examined. Selected review articles were used to highlight points made, but not to draw inferences. A few important studies reported before 1966 and between July 1996 and January 1997 were also added to the search results. We excluded studies that evaluated the collection, processing, storage, testing and other laboratory concerns related to RBCs. Disagreement was resolved through consensus.

Data synthesis

The selected articles were categorized according to topic and study design as defined by Meinert[16] (Table 1). Studies were also assigned a level of evidence as proposed by Cook and colleagues[17]; i.e., inferences from clinical studies evaluating therapeutic interventions should be considered very weak if they are derived from case series (level V) and strong if derived from a large randomized, controlled clinical trial (RCT; level I). Evidence-based inferences were then formulated and graded according to the scale proposed by Wilson and

Table 1: Definitions of the various study designs

Types of studies	Description
Interventional studies	
Randomized trial; randomized, clinical trial	Experiment in which patients are randomly allocated to receive or not receive an experimental preventive, therapeutic or diagnostic procedure, then followed to determine the effect of the intervention.
Non-randomized, controlled trial	Experiment in which assignment of patients to the intervention group is at the convenience of the investigator or according to a preset plan that does not conform to the definition of random.
Before–after trial	Investigation of therapeutic alternatives in which patients at one time and under one treatment are compared with patients at a subsequent time, treated in a different fashion. If the disorder is not fatal and the "before" treatment is not curative, the same people may be studied before and after treatment, strengthening the design.
Observational studies	
Nonconcurrent cohort study; retrospective cohort study	A follow-up study of a cohort from a point in the past to a more recent point in the past or to the present using existing data, e.g., information in their medical records.
Cross-sectional study; cross-sectional survey	A nonexperimental study involving observation of a defined population at a single point or over a narrowly defined time interval.
Case series	A series of patients with a defined disorder; the term is usually used to describe a study reporting on a collection of patients treated consecutively in a similar manner, without a concurrent control group.
Case–control study; retrospective study	Study generally used to test possible causes of a disease or disorder, in which people with a specific disorder are compared with people who do not have the disorder with respect to previous or current exposure to a putative causal factor.
Other studies	
Guideline	A statement of policy or procedure issued to serve as guide in a specified setting or application.
Review	A general survey of previous work or materials, for example in relation to preparing an article for a journal.

Source: Adapted from Meinert.[16]

co-workers,[18] who described a 6-point scale in which recommendations are based on the type of design, the degree of similarity between study results and whether confidence intervals (CIs) overlap a treatment threshold. A grade A1 recommendation is based on more than 1 RCT with similar outcomes, all indicating that an intervention either does or does not result in clinically important benefits. A grade C2 recommendation, the weakest rating, is based on observational studies that do not have comparable outcomes.

Results

There were 189 primary studies identified for this review. We also incorporated non-peer-reviewed data from annual reports of the Canadian Red Cross Society, Blood Services, between 1981 and 1994.[19] We excluded technical and laboratory studies (n = 9), reviews (n = 42), guidelines (n = 16) and commentaries (n = 9).

Of the 189 articles, 78 (41%) were interventional studies: 48 were RCTs, including 23 studies of hemodilution; 8 studies evaluating quality of life and symptoms such as dyspnea, fatigue and exercise tolerance;[20–27] 8 studies of immunosuppressive complications from RBC transfusions (i.e., nosocomial infections and cancer recurrence);[28–35] 6 on transfusion strategies;[36–41] 2 on educational interventions;[42,43] and 1 on a blood conservation device.[44]

Interventional studies also included 14 (9%) before–after trials primarily examining RBC utilization. Investigators evaluated education programs,[45–48] a monitoring program,[49] clinical recommendations,[50] statewide informed consent legislation,[51] regulatory policies[52,53] and an autologous blood program.[54] There were also 4 nonrandomized or concurrent control trials that examined the determinants of RBC blood requirement.[55–58]

Under interventional studies, we also included nonrandomized/concurrent control trials (n = 8) and interventional studies with historical controls (n = 8) that covered a broad range of clinical transfusion issues.

Among the 111 observational studies (59% of total), 60 (32%) were cross-sectional surveys, 27 (14%) were cohort studies (7 prospective and 20 retrospective), 18 (10%) were case–control studies and 6 (3%) were case series. The cross-sectional studies employed various designs including audits (n = 35), self-administered physician surveys (n = 8) and secondary analyses of administrative databases (n = 17). Most of these studies addressed issues related to RBC utilization. Physician surveys generally focused on transfusion triggers and determinants of transfusion practice.[59–66] Of the prospective cohort studies, 2 examined indications for RBC transfusion,[67,68] 3 addressed the effectiveness of educational strategies[69–71] and 2 focused on algorithms to control RBC utilization.[72,73] Finally, 20 retrospective cohort studies addressed RBC utilization,[74–78] cost of transfusions[79–83] and the effects of educational tools[84] and control measures[85,86] on transfusion practice; the 7 remaining studies examined various issues related to RBC utilization using case–control and case series designs.

From the systematic evaluation, 19 inferences were drawn and graded according to the strength of supporting evidence (Table 2). Among these, 2 were not supported by any report and 7 were drawn only from observational or analytical studies (grade C). The inference supported by the strongest evidence (grade A) involved educational outreach programs and the use of intra-operative algorithms.

Table 2: Inferences from the clinical practice literature

Inference	Grade*
RBC transfusions have decreased since the mid-1980s	C1
Significant institutional variation in RBC transfusion practice has been consistently observed in a number of clinical settings	C1
There is significant variation in RBC transfusion practice among physicians	C1
There is significant institutional red cell transfusion practice variation	C1
The unnecessary use of RBC transfusion is frequent	C1
The rate of appropriateness of red cell transfusion varies from study to study	C1
The use of a transfusion trigger or threshold of [Hb] 100 g/L by practitioners has declined in recent years	NE
A transfusion threshold of [Hb] 100 g/L is optimal in high-risk patients	B1
A transfusion threshold between [Hb] 70 g/L and 80 g/L is optimal in all patients, independent of risk	B2
An increased risk of adverse outcomes from anemia has been reported in patients with coronary artery disease	C1
Other forms of heart disease may also be risk factors in anemic patients	NE
An increased risk of adverse outcomes from anemia has been reported in patients with cerebrovascular disease	B2–C1
An increased risk of adverse outcome from anemia has been reported in patients with respiratory disease, advanced age and increased illness severity	C2
Quality of life improves with increasing [Hb] in anemic patients	B2
Symptoms including dyspnea, fatigue and exercise capacity improve with increasing [Hb]	B2
Postoperative infections are more likely in patients receiving allogeneic RBCs	B2
There is no relationship between [Hb] and the frequency of sickle-cell crises	A1
Educational outreach programs improve RBC utilization and appropriateness of transfusion	A1–A2
The use of intra-operative algorithms increases appropriate use of blood products	A1–A2

*NE = no clinical evidence, i.e., insufficient data to grade the inference; A1 = randomized, controlled clinical trials (RCTs), no heterogeneity, 95% CIs all on 1 side of threshold number needed to be treated (NNT); A2 = RCTs, no heterogeneity, CIs overlap threshold NNT; B1 = RCTs, heterogeneity, CIs all on 1 side of threshold NNT; B2 = RCTs, heterogeneity, CIs overlap threshold NNT; C1 = observational studies, CIs all on 1 side of threshold NNT; C2 = observational studies, CIs overlap threshold NNT.

Discussion

What are the indications for allogeneic RBC transfusions?

The Canadian Red Cross Society's *Clinical Guide to Transfusion*[10] states that the chief indication for RBC transfusion is anemia, mainly to increase O_2 delivery, not solely to expand intravascular volume without evidence of decreased [Hb].

Other major medical organizations have also developed guidelines or position statements with similar indications.[2,3,8,13,87] Many of the guidelines provide more specific criteria for the use of allogeneic RBCs. The American College of Physicians added that an empiric transfusion threshold should be avoided, that RBCs should be administered to relieve symptoms and on a unit-by-unit basis. They also explicitly stated that RBCs are contraindicated as a means to enhance well-being and promote wound healing.

Many guidelines and position papers[3,4,8,87–89] have also suggested a specific [Hb] or range of values to guide the transfusion decision: the National Institutes of Health[4] suggest [Hb] 70 g/L; two separate publications of the American Association of Blood Banks (both developed as audit criteria not clinical practice guidelines)[8,87] propose 80 g/L; and the American Society of Anesthesiologists[3] states that RBC transfusion will provide the greatest benefit when [Hb] is 60 to 100 g/L.

However, the indications from these many sources may not be useful to practitioners because of limitations in the evidence and their inability to determine the ideal rate of O_2 delivery for a particular patient and to identify patients at increased risk of either anemia or transfusion.

Have there been changes in clinical transfusion practice and utilization of RBCs over time?

For decades, a [Hb] of 100 g/L or a hematocrit of 30% was advocated as the threshold or transfusion trigger at which most patients with acute anemia should be administered RBCs without any consideration of the patient's clinical course.[1,90–93] Zauder[94] surmised that the popular 100 g/L threshold originated in a discussion of preoperative anemia in a 1941 publication by Adams and Lundy.[95] Subsequently, Clark and colleagues[96–98] described a condition they labeled as chronic shock in chronically anemic patients. These authors went on to say that such patients should be transfused when their [Hb] decreased below 100 g/L.

Throughout the 1950s and 60s, most major anesthesia and surgical textbooks incorporated the notion of a 100 g/L transfusion trigger.[95] In 1945, Brannon and colleagues[99] documented incremental increases in cardiac output in anemic patients with [Hb] below 100 g/L and interpreted this observation as potentially detrimental. In a series of studies on hemodilution, Messmer and coworkers[100–105] concluded that a hematocrit of 30% (or [Hb] of 100 g/L) provides maximal O_2 delivery. A 1970 study[106] found an association between increased mortality and [Hb] below 100 g/L.

More recently, clinical practice guidelines from major medical organizations[2–4,8,13,107,108] have refuted the concept of a single [Hb] as a transfusion threshold, emphasizing the need for clinical judgement in transfusion-related decisions. Recent reviews[90,92,93,109] have also concluded that insufficient evidence exists to support a single [Hb] threshold.

Although experts have recommended moving away from the use of transfusion triggers or thresholds, practitioners appear to be slow in modifying their approach to allogeneic transfusions. Several self-administered surveys have examined the use of triggers.[59,60,62–64] In 1970, the first such survey[59] reported that 88% of anesthesiologists required a [Hb] of at least 90 g/L prior to surgery and 44% required a concentration greater than 100 g/L. In 1987, a self-administered survey of American anesthesiologists[60] revealed that 65% required a preoperative [Hb] of 100 g/L. A 1992 Canadian survey of critical care practitioners[62] observed that 35% of respondents identified 90 g/L as minimum concentration and an additional 40% selected 100 g/L. The authors also noted significant difference in pretransfusion [Hb] among the 4 clinical scenarios (normovolemic ventilated patients with severe sepsis, trauma, gastrointestinal bleeding and postoperative vascular surgery) and a number of potential risk factors including age, disease severity, hypoxia acidosis and myocardial ischemia. In a recent survey of gynecologic oncologists,[64] most respondents reported that they adopted very low transfusion thresholds which varied considerably according to the clinical setting.

From these studies, it appears that a proportion of physicians tolerated increasing levels of anemia in their patients. Because of differences in study populations, study designs and quality of the methods used, it is not possible to infer that physicians have modified their practice over time or have incorporated recommendations from published guidelines into their clinical practice.

Trends noted in clinical transfusion practice have been mirrored by significant changes in utilization rates. Several American studies,[110–119] 1 Taiwanese[120] and 1 older British study[7] have documented trends in the administration of RBCs. The British study described a 13.5% increase in the number of units transfused from 1954 to 1958 in a section of London. Between 1948 and 1960 at the Cleveland Clinic, there was a 4-fold increase in the

number of units transfused.[110] In Connecticut,[114] the use of allogeneic RBCs increased between 1966 and 1976. Three National Institutes of Health (NIH) surveys[117–119] indicated that the number of transfusions in the United States doubled from 1971 to 1980. From 1980 to 1986, transfusion rates increased only minimally and dropped significantly in 1987.[121] Wallace and colleagues[112,116] reported a 3.1% decrease from 1989 to 1992. Overall, surveys in the United States suggest that the rate of RBC transfusions increased until the mid-80s and subsequently declined. These estimates should be interpreted with caution given that the data used for examining longitudinal trends were gathered from cross-sectional surveys rather than through prospective studies.

Unfortunately, there are no published Canadian studies describing trends over time. Data from Canadian Red Cross Society annual reports[19] show that the number of RBC units transfused increased between 1980 and 1986, stabilized until 1991, then declined steadily until 1995. In 1995, 856 267 RBC units were collected whereas 757 674 (88.5%) were transfused. There also appears to have been a decrease in the number of allogeneic RBC units administered from 3.01 to 2.82 units per patient between 1991/92 and 1994. These data, gathered by a single national organization in a similar fashion from year to year, confirm observations based on published estimates in the United States.

In summary, significant changes have occurred, both in the clinician's approach to RBC administration and in overall utilization in the past 3 decades. The more conservative approach to transfusion practice and the decline in RBC use in Canada since the mid-1980s have coincided with the advent of HIV detection in allogeneic RBCs.

Which patients are most frequently transfused with allogeneic RBCs?

A number of studies describe the overall patient population receiving RBC transfusions,[85,122–126] and a significant number of studies described RBC utilization in selected patient populations.[47,48,50,51,53,55,65,76,77,127–139] In a 1992 survey conducted in 45 Toronto area hospitals, 65% of the allogeneic RBCs used were administered to patients undergoing operative procedures categorized as digestive and abdominal, cardiovascular and musculoskeletal.[122] Brien and co-workers[123] reported that 56% of all RBC units were administered to surgical patients whereas Ghali and colleagues[85] determined that 69% of RBC units are transfused into surgical patients.

In general, cardiac surgical procedures, orthopedic procedures (e.g., total hip and knee replacement) and selected gynecologic (e.g., radical hysterectomy) and urologic procedures (e.g., radical prostatectomy) were noted to have a high proportion of patients requiring RBCs.[54,122,125,140] The proportion of patients receiving RBCs ranges from 50% to 80% for aortic aneurysms and coronary revascularization to as few as 2%–6% for cholecystectomy.[54,122,130] In nonoperative settings, allogeneic RBCs were most frequently administered to patients with malignancies.[122] Despite the lack of optimal study designs describing trends over time and utilization in various patient populations, published studies appear to be remarkably consistent.

Is there published evidence of significant practice variation in the use of RBCs?

Several clinical studies have commented on the appropriateness[45,56,84,85,123,125,141–145] and practice variation[114,124,128,129,138,146–148] in RBC use. Several investigators identified practice variation as being an interinstitutional phenomenon. A secondary analysis of a large database conducted in 1978[114] found striking variation among hospitals in Connecticut: large hospitals used more blood and plasma per discharge than smaller ones. The authors inferred that physician habits and personal preferences determined institutional variation in blood utilization. However, others criticized the study for failing to control for the effects of case mix.[1] Subsequently, other studies have documented significant practice variation within specific disease categories,[146,147] clinical settings[149] and surgical procedures[128,129] including hip[130,132,150,151] and knee[132,150,151] arthroplasty and coronary revascularization.[138,139,148]

Controlling for population differences, blood loss and pump time, a prospective audit of patients undergoing coronary artery bypass grafting[148] identified transfusion factors, such as the nadir and discharge hematocrits, that accounted for significant variation in blood use among 18 tertiary care hospitals. In similar patients, Surgenor and colleagues[138] found that there were significant differences between hospitals in the percentage of patients transfused. Hébert and co-workers[149] found a significant variation in transfusion practice (in terms of lowest [Hb]) among 6 Canadian intensive care units after controlling for the effects of disease severity, diagnosis, age and sex.

Retrospective chart reviews and self-administered surveys have also been carried out to determine whether physicians account for significant variations. In the Sanguis study,[129] transfusion rates were found to depend more on physicians than the patient population, type of procedure or hospital. Wide variation was found among 43 hospitals in 10 European countries[128] and between hospitals within the same country. Some factors found to

influence this variation were age, sex, preoperative hematocrit and blood loss. In a survey of anesthesiologists, Stehling and colleagues[60] observed a wide variation in the use of a transfusion trigger of [Hb] 100 g/L. The variations depended more on the institution and physician than on patient characteristics.

There is substantial evidence that transfusion practice varies. Many authors have concluded that such differences suggest inappropriate use by physicians. However, there are few, if any, studies that explore the reasons for these observations. It is possible, for example, that the limited number of large RCTs as well as competing risks elaborated in the existing evidence may be a significant source of variation.

Is there evidence of unnecessary use of RBCs?

Despite significant differences in both criteria and reported rates, studies consistently show that a proportion of transfusions are unnecessary (Table 3). Criteria for appropriateness included selected guidelines,[45,85,141,152] clinical indicators,[144,153] specific [Hb],[69,127,144,154] algorithms,[84,123] some combination of these[142] or other criteria.[56]

The rates of unnecessary or inappropriate RBC use range from 4% to 66%.[1] In a Canadian teaching hospital, in which 55% of 170 allogeneic RBC transfusions were deemed inappropriate,[85] most unnecessary transfusions were in normovolemic, hemodynamically stable patients with anemia and multiple-unit transfusions. Brien and colleagues[123] determined that 67% of family medicine patients to 95% of obstetrics–gynecology patients were transfused according to appropriate indications. In several studies, there were differences in rates of appropriateness between men and women.[56,132,138,139,156,157] Because they had a lower baseline [Hb], a greater proportion of women were transfused as [Hb] fell below an arbitrary transfusion trigger.

In explaining these observations, 1 study[61] suggested that more junior staff were often coerced to transfuse patients unnecessarily by attending physicians. The authors also noted that attending physicians exhibited more widespread deficiencies in their knowledge of transfusion risks and indications. Differences in study designs (audits versus secondary analysis of databases), sample size, study population (diagnostic category or procedure, age and sex differences and disease severity) and appropriateness criteria may all account for the variation in the rates of unnecessary RBC use. Indeed, Hasley and co-workers[158] and Goodnough and colleagues[56] noted a relation between the use of restrictive criteria and the increased number of inappropriate transfusions. Difficulty with missing or incomplete data, preconceived biases, and any number of measurement biases weaken any inference drawn from these retrospective studies attempting to evaluate bedside decisions.

Several approaches have been used to improve transfusion practice. In an RCT,[43] focused teaching sessions decreased noncompliance with transfusion guidelines by 40% among surgeons in the study group compared with a 9% increase in the control group. Despotis and colleagues[42] evaluated an intra-operative transfusion algorithm in patients experiencing microvascular bleeding after cardiac surgery and found significant effects on transfusion practice. Patients treated according to the algorithm had fewer exposures to red blood cells and other blood components than patients treated according to standard policy. The algorithm had a significant impact on surgeons' transfusion practice, assisted in decision-making and served as an effective teaching tool.

Interventions that directly affect clinical decision-making, such as clinical practice guidelines, education programs, conferences, academic detailing and audits, may improve a physician's transfusion practice. A number of other interventions, involving various levels of the health care and blood system, may modify clinical decision-making (Table 4). However, in many instances, the impact of each method on transfusion practice, alone or in combination, has not been evaluated.

What are the relative benefits, risks, harms and costs associated with anemia and allogeneic RBC transfusions?

In the treatment of anemia, all clinically important potential benefits, risks and costs must be considered in decisions to adopt one approach over another. One should also consider whether alternative therapies such as preoperative autologous donations and pharmacologic interventions, including aprotinin and erythropoeitin, should replace or be incorporated into any transfusion strategy. Thus, the practitioner should weigh the risks of anemia against the benefits and risks of administering allogeneic RBCs (or alternatives). Ideally, rigorously conducted RCTs in patients with anemia should compare approaches and interventions to provide clinicians with the most accurate estimates of treatment benefit.[16,17,159]

To develop an optimal treatment approach in patients with anemia, RCTs should first compare outcomes such as mortality and myocardial infarction rates in a variety of clinical settings (i.e., perioperative anemia and anemia in the critically ill) and diseases (patients with and without cardiac disease). More subjective but equally important outcomes should also be examined. Comparisons should include health-related quality of life, activity levels and exercise tolerance as well as symptoms including fatigue, dyspnea and exercise tolerance. Other outcomes

Table 3: Studies evaluating the appropriateness of transfusions

Study	Design	No. of subjects	Study population	Evaluation criteria	Proportion of unnecessary transfusions	Comments
Diethrich[69] (1965)	Retrospective review	217	Medical, surgical and ob/gyn patients	- [Hb] < 100 g/L - Acute blood loss with signs of hypovolemia - Blood loss > 500 mL	25% of multiple units 60% of single units	- Practice in single-unit institutions - Prospective evaluation - Unnecessary transfusion greatest in ob/gyn patients
Reece and Beckett[154] (1966)	Retrospective review	2921	Adult patients in community hospital	- Abnormal Hct - Single-unit transfusion	66% of units transfused	- Focused on single-unit transfusion - Ob/gyn patients most frequently given single-unit transfusion
Freedman[127] (1978)	Analysis of database	3616	Anemia in nonoperative patients	- [Hb] 100 g/L	13.8% of transfusion episodes	- Difficult to determine accuracy of data
Stehling and Esposito[45] (1989)	Retrospective review	627	Intra-operative patients	- Hct < 30% - Estimated blood loss > 15% of blood volume	Year 1, 26% Year 3, 3%	- Conducted over several years - Appropriateness improved over time - Large study - Simple criteria - Review of all blood products
Coffin et al[84] (1989)	Retrospective review	156	Medical and surgical patients	- Algorithms (criteria maps) for blood and blood product transfusion	4% of units transfused	- Series of criteria in complex algorithms
Brien et al[123] (1989)	Retrospective review	297	All patients in tertiary care hospital	- Active hemorrhage - Chemotherapy-induced anemia - Cardiopulmonary compromise - Transfusion dependence	12% of units transfused	- Criteria vague and not reproducible
Goodnough et al[55] (1992)	Retrospective review	525	Orthopedic patients	- Blood loss of 10%, 20% or 30% of blood volume	25%, 42% and 60%, respectively	- No assessment of clinical factor other than blood loss - Transfusion trigger different in women
Saxena et al[142] (1993)	Retrospective review	438	Medical patients at 1 community and 1 teaching hospital	- No specific Hct - Anemia with signs of hypovolemia - Anemia with cardiac or respiratory disease	35% of transfusion episodes	- More unjustified transfusions in community hospital - Criteria not reproducible - At least 2 independent reviews of each medical record
Goodnough et al[155] (1993)	Retrospective review	498	CABG patients	- Estimated blood loss > 10% of blood volume	18% of units transfused	- Study done to assess impact of conservation strategies - Criteria limited to blood loss; difficult to apply prospectively
Ghali et al[85] (1994)	Retrospective review	55	Medical and surgical patients	- Need for transfusion according to ACP guidelines	55.3%	- Small study - Limited to 1 institution - ACP guidelines not designed for audits
Metz et al[131] (1995)	Retrospective review	200	Consecutive patients in tertiary care hospital	- [Hb] < 70 g/L - [Hb] 70–100 g/L and various clinical indications - Perioperative [Hb] ≤ 80 g/L - Excessive (abnormal) bleeding at operation	16% of transfusion episodes 10% of units transfused	- Also reviewed platelet and plasma transfusion - Criteria based on ACP guidelines
Corwin et al[152] (1995)	Retrospective review	142	ICU patients with length of stay > 1 week	- Active bleeding or surgery - Hct < 25% - Low cardiac output - Myocardial infarction/ischemia - Oxygen transportation - Renal ischemia - Preoperative - Adapted from NIH consensus conference	29% of transfusion episodes	- Criteria vague and not reproducible - Many transfusions administered because of arbitrary trigger - Diagnostic blood tests result in significant blood loss in ICU
Mozes et al[144] (1995)	Retrospective review	383	All patients from tertiary care hospital	- Symptomatic refractory anemia - Symptomatic cardiovascular disorders with anemia - Hct < 26% with history of cardiovascular disorders - Preoperative Hct < 26%	57.7% of transfusion episodes	- Unnecessary use greatest in end-stage renal failure and terminal cancer - Also reviewed platelet and plasma transfusion

Note. [Hb] = hemoglobin concentration; Hct = hematocrit; CABG = coronary artery bypass grafting.

to be considered include the rates of viral transmission and infectious complications following various allogeneic RBC transfusion strategies.

We identified 6 RCTs contrasting 2 transfusion strategies in a total of 813 patients (Table 5).[36–41] Only 1 study, conducted in patients with sickle-cell disease, was large enough to rule out clinically important differences in its primary outcome, perioperative sickle-cell crises.[40] In this study, an aggressive transfusion strategy, compared with a more conservative regimen, was unable to prevent sickle-cell crises.

In a second study, 50 consecutive patients with severe gastrointestinal bleeding were randomly chosen to receive at least 2 allogeneic RBC units immediately or no transfusions unless [Hb] fell below 80 g/L.[41] In the immediate-transfusion cohort, 9 patients had a recurrence of gastrointestinal bleeding compared with 1 patient in the delayed-transfusion cohort ($p < 0.001$).

Patients undergoing coronary revascularization were examined in 2 studies.[36,37] In 1,[37] there was no difference in postoperative complication rates between patients treated with a liberal transfusion strategy compared with those subjected to a conservative strategy, although for the conservative group there was a significant decrease in total postoperative blood use. The other[36] assessed day 5 exercise tolerance as well as hemodynamic and myocardial metabolic response following normovolemic hemodilution in 27 patients. One group of 13 patients received RBCs if their [Hb] fell below 120 g/L in addition to colloids; the other 14 patients received crystalloids and allogeneic RBCs only if [Hb] fell below 70 g/L. Although patients in the low [Hb] trigger group received significantly fewer RBCs than the other group, there were no differences in morbidity, mortality or exercise tolerance. In a small subset of 6 patients, there were differences in the rate of myocardial lactate recovery in the low [Hb] trigger group suggesting increased myocardial ischemia from anemia.

Table 4: Potential strategies to decrease exposure to allogeneic blood

Category	Strategy
Health systems and policies	• Disbursement of funds (financial constraints have an impact on resource allocation and availability of alternatives) • Collection, product testing and processing (affect infectious and noninfectious risks, thus safety of product)
Medicolegal	• Informed consent legislation (may increase awareness of risk, thereby decreasing exposure) • Case law and liability (may change physician transfusion practice)
Institutional	• Audits and utilization reviews by multidisciplinary transfusion committee • Evaluation of transfusion programs including the use of alternatives • Development and dissemination of clinical practice guidelines (or adaptation of existing ones) • Informed consent policy
Physician and allied health professionals	• Educational interventions • Clinical practice guidelines • Statements by opinion leaders • Critical paths or treatment algorithms • Dissemination of research and quality assurance studies • Peer and public pressure • Case law and litigation • Review of individual transfusion practice
Alternative transfusion strategies	• Perioperative autologous transfusion • Hemodilution • Directed donations • Modifications in transfusion practices (i.e., greater tolerance of anemia)
Blood conservation techniques	• Fewer blood tests • Less blood used for tests • Changes in surgical procedures and techniques • Decrease perioperative use of anticoagulants and antiplatelet agents • RBC salvage
Pharmacologic interventions	• Agents to decrease surgical bleeding (e.g., aprotinin, DDAVP) • Agents to increase RBC mass (e.g., erythropoeitin) • Blood substitutes
Research	• Program evaluation • Behavioural and educational interventions • Transfusion strategies • Clinical studies of new or existing pharmacologic interventions • Clinical studies evaluating devices

RBC = red blood cell; DDAVP = Desmopressin acetate or arginine vasopressin.

Table 5: Randomized, controlled clinical trials evaluating transfusion strategies

Study	Level of evidence	No. of patients	Study population	Interventions	Outcomes	Comments
Weisel et al[26] (1984)	II	27	CABG	Crystalloid alone *(n = 14)* v. blood or colloid solutions *(n = 13)*	- [Hb] lower in crystalloid group 20 h postoperation ($p = 0.01$) - Reduction in blood utilization in the crystalloid group - No difference in pulmonary edema and hemodynamic parameters (cardiac index and filling pressures)	- Small sample size - No difference in mortality or myocardial infarction rates - Delayed recovery of myocardial oxygen and lactate extraction in a small number of patients in the crystalloid group.
Johnson et al[27] (1992)	II	38	CABG	Conservative group Hct maintained at 25% *(n = 20)* v. liberal group Hct maintained at 32% *(n = 18)*	- Conservative group transfused with fewer units than the liberal group ($p = 0.012$) - Mean cardiac index same for both groups in the OR and 1 day postop - Mean postop LOS: 7.6 ± 1.9 days (liberal), 7.9 ± 4.3 days (conservative) - No difference in fluid requirement, hemodynamic parameters or hospital complications - No relation between exercise tolerance on the 5th and 6th days and Hct	- Small sample size - No postoperative deaths reported - No difference in ischemic event
Blair et al[41] (1986)	II	50	GI hemorrhage	At least 2 units of PRCs (immediate) *(n = 24)* v. no transfusion unless [Hb] < 80g/L (delayed) *(n = 26)*	- Decrease transfusions in delayed group (2.6 v. 4.6 units/patient, $p < 0.05$) - The number of re-bled patients was greater in the immediate transfusion group (9 v. 1, $p < 0.01$)	- Small sample size - Study design included a pilot study - Laboratory and clinical measurements available - No detailed data related to operative interventions and mortality rate - Prolonged clotting time and higher re-bleeding rate due to blood transfusions in the first 24 hours
Fortune et al[28] (1987)	II	25	Adult trauma	Hct = 30% *(n = 12)* v. Hct = 40% *(n = 13)*	- 5 units of PRC more in Hct = 40% group - No difference in hemodynamic parameters - Higher intrapulmonary shunt in Hct = 40% group	- Small sample size - Physiologic outcome measurements only - No data on mechanisms and type of traumatic injury - No data on clinical outcomes
Hébert et al[39] (1995)	II	69	ICU	Restrictive group: [Hb] = 70–90 g/L *(n = 33)* v. liberal group: [Hb] = 100–120 g/L *(n = 36)*	- Average daily [Hb] = 90 g/L v. 109 g/L ($p < 0.001$) - Number of units tranfused 48% less in restrictive group (2.5 v. 4.8 units/patient) - No difference in mortality and organ failure rates ($p > 0.05$) - No difference in ICU and hospital LOS ($p > 0.05$)	- Small sample size - Pilot unable to detect difference in clinically important outcomes
Vichinsky et al[40] (1995)	I	604	Sickle-cell disease in surgery	Aggressive *(n = 303)* v. conservative *(n = 301)* regimens	- No difference in life-threatening complication rates but more transfusion-associated complications, i.e., hemolytic reactions and alloantibodies in the aggressive group	- Total of 551 patients undergoing 604 operations - Randomized procedures not patients - Study in a specific population. - Only 1 patient died in all procedures

Note: [Hb] = hemoglobin concentration; LOS = length of stay; GI = gastrointestinal; CABG = coronary artery bypass grafting; ICU = intensive care unit; PRC = packed red cells.

Hébert and colleagues[39] randomly assigned 69 critically ill patients to a restrictive or liberal RBC transfusion strategy to evaluate the impact of the treatments on mortality rates, organ dysfunction scores and other markers of morbidity. Neither mortality nor the development of organ dysfunction were affected by the transfusion strategy. However, maintaining [Hb] between 70 and 90 g/L decreased the average number of units transfused from 4.8 to 2.5 (48% reduction, $p < 0.001$).

Finally, 25 critically ill trauma victims were randomly chosen to receive allogeneic RBC transfusions once hematocrit levels reached either 30% or 40%.[38] The authors concluded that there were no discernable differences in O_2 transport variables between the 2 groups.

In summary, 5 of the 6 studies enrolled too few patients to make significant inferences regarding important outcomes from RBC transfusions and the 1 large RCT reported only the effects of transfusions using a disease-specific outcome in sickle-cell disease.

A total of 23 RCTs evaluating perioperative hemodilution in patients undergoing the following surgical procedures were identified: cardiac surgical interventions (primarily coronary revascularization),[160–170] vascular procedures,[171–173] tumor resection,[174,175] hip arthroplasty,[176–179] thoracic procedures[180] and prostate resection.[181,182] Of these 18 studies reported the number of units or volume of allogeneic RBCs used; and 12 reported allogeneic RBC exposure rates. The remaining studies focused on oxygen transport as well as the cardiac and coronary effects of this intervention (see Hébert and associates, Review of physiologic mechanisms in response to anemia, this issue).

In the 12 studies reporting a statistically significant difference in allogeneic RBC transfusion volumes, the decrease was small and clinically unimportant (250–500 mL of RBCs). Thus, the efficacy of perioperative hemodilution in limiting allogeneic RBC exposure has yet to be established. In addition, inferences about the safety of anemia based on these studies are limited because the technique is used in highly selected patients in a controlled setting; intra-operative transfusion threshold and protocols were not explicitly outlined, therefore the degree of anemia is not known; and the techniques (including degree of hemodilution, replacement fluids, storage and reinfusion) were not comparable from 1 study to another. The lack of significant differences in cardiac events or mortality rates in these small studies should not be interpreted as inferring that moderate degrees of intra-operative normovolemic anemia are safer than avoidance of anemia through RBC transfusion.

Several observational studies were also identified, including numerous reports of toleration of severe anemia in terms of mortality risk and adverse consequences such as myocardial infarction in surgical patients.[91,106,183–193] In a prospective study of 1769 anemic patients undergoing coronary revascularization, Bayer and co-workers[183] found that a decreased hematocrit (27% to 30%) was well tolerated, with no reported increase in either morbidity or mortality compared with historical controls from the same institutions. Additional reports or case series[91,190,194–196] describe successful outcomes in patients with chronic anemia as a result of renal failure.

Finally, descriptive studies in patients refusing RBC transfusion[184–186,191,192] and in regions where blood supplies have been limited[187,197] have demonstrated that patients can survive surgical interventions with [Hb] as low as 45 g/L. Two studies, 1 case–control[185] and 1 case series,[186] in the same cohort of Jehovah's Witness patients[191] documented an association between preoperative [Hb], intraoperative estimated blood loss and postoperative mortality. No deaths were reported in more than 100 patients undergoing major elective surgery when preoperative [Hb] was greater than 80 g/L and estimated blood loss was less than 500 mL. In a single-centre series of 542 Jehovah's Witness patients undergoing a cardiac surgical procedure, the overall mortality was 10.7%; only 2.2% of the deaths were considered to be a direct consequence of anemia.

In summary, these observational studies suggest that moderate degrees of anemia are well tolerated in low-risk patients. However, such studies only provide weak evidence in support of a lowered transfusion threshold given the potential for selection and measurement biases as well as the possibility of significant confounding by clinical factors such as disease severity and comorbid diseases. Although a significant number of articles have examined the impact of various transfusion strategies on clinically important outcomes such as mortality and rates of myocardial infarction, few were considered to be level I or II RCTs. In addition, the clinical heterogeneity of patient populations and interventions would not permit the use of meta-analytic techniques to combine the results of the RCTs.

Determining the relative benefit of RBC transfusions should include not only an assessment of mortality, but also consideration of the impact of therapy on anemia-related symptoms such as dyspnea and fatigue and overall measures of health status such as quality of life. This is most relevant in patients with chronic anemia and patients at low risk of death from acute anemia. We were unable to identify any RCT comparing the effect of various [Hb] or transfusion strategies on symptoms, physical functioning or health-related quality of life. The most compelling evidence supporting an association between [Hb] and quality of life arises from studies evaluating erythropoeitin use in a number of clinical set-

tings[20–25] (Table 6). Improvements in health-related quality of life were observed in patients on hemodialysis,[21–23,198] in those with chronic anemia as a result of human immunodeficiency virus (HIV) or HIV therapy[24] and those with cancer-related anemia.[25,199]

The greatest benefit of increased [Hb] in erythropoeitin therapy appears to be in terms of increased energy and activity levels.[21,24,198] Using a disease-specific quality of life instrument, hemodialysis patients in the Canadian Erythropoeitin Study[22] reported significant improvements in their scores for fatigue and physical symptoms without significant changes in exercise capacity assessed using the 6-minute walk test. In contrast, an RCT[26] evaluating iron therapy in anemic women did not report any improvement in fatigue and breathlessness despite significant increases in [Hb]. In another study,[27] psychomotor function in anemic women was also found to be unaffected by iron therapy. Therefore, there are conflicting conclusions regarding the association between anemia and subjective outcomes that have arisen from well-controlled clinical trials evaluating interventions other than RBC transfusions.

When considering transfusion with allogeneic RBCs, the physician must weigh the consequences against the risks associated with ongoing anemia. Many of the risks associated with allogeneic RBC transfusions have been difficult to quantify because they are very small. However, the risk of transmitting viruses such as HIV and hepatitis has been uppermost in the minds of practitioners and the public in the past few years. Currently, the risk of contracting a viral infection from a unit of blood ranges from 1:63 000 for hepatitis B and 1:103 000 for hepatitis C to as low as 1:676 000 for HIV and 1:641 000 for human T-cell lymphotropic virus (types I and II) based on a recent American study[200] and Canadian Red Cross Society data.[19]

There are no prospective cohort studies describing the rates of viral transmission and associated complications in recipients of blood products. In addition, the donor population is constantly changing and the screening process evolving. New diseases or mutations of older diseases are continually threatening the system. These risks are difficult to quantify and incorporate into decision-making. A number of other potential complications include hemolytic reactions — acute (1 in 25 000 units transfused) and delayed (1 in 2500–9000) — anaphylaxis (1 in 20 000–50 000), transfusion-related lung injury, graft-versus-host disease, posttransfusion purpura, congestive heart failure (1 in 100) and iron overload (begins after more than 20 RBC units transfused).

Many investigators have studied and commented on the immunosuppressive effects of allogeneic RBC transfusion.[201–220] Observational studies[201,207,221,222] have suggested an association between the administration of allogeneic RBCs and the recurrence of cancer as well as postoperative infections. It has been hypothesized that a unit of allogeneic blood depresses immune function, thereby increasing a host's susceptibility to infections and promoting tumour growth.

We identified 8 RCTs evaluating the immune consequences of RBC transfusions, contrasting either rates of cancer recurrence ($n = 2$) or postoperative infections ($n = 6$). Investigators compared either leukocyte-depleted[28–33] or autologous[34,35] transfusion with allogeneic RBC transfusion. Contradictory conclusions were drawn from the 6 RCTs examining postoperative infections (Table 7). Two studies[28,34] did not find any significant difference in the rates of infection among patients who had undergone colorectal surgery. Houbiers and colleagues[28] found a higher rate of postoperative infection in patients receiving leukocyte-depleted as opposed to allogeneic RBCs (42% versus 36%, $p > 0.05$). However, the 4 remaining studies[29,32,33,35] reported clinically important decreases in postoperative infections in patients receiving leukocyte-depleted RBCs compared with standard allogeneic RBC products.

In a recent RCT, Jensen and colleagues[29] demonstrated that the rates of wound infections and intra-abdominal abscesses were significantly lower in patients receiving allogeneic RBCs compared with untransfused groups (12% v. 1%, $p < 0.0001$). The frequency of pneumonia was also lower in patients receiving leukocyte-depleted RBCs (3%) or no transfusions (3%) compared with patients receiving allogeneic transfusions (23%, $p < 0.001$).

In summary, the 6 level-I studies arrived at divergent conclusions concerning the risks of postoperative infections attributed to allogeneic RBC transfusions. A meta-analysis using either aggregate or individual patient data might provide useful insights from these 6 conflicting RCTs.

The 2 studies evaluating cancer recurrence have not convincingly demonstrated that allogeneic RBCs truly affect the rates of tumour recurrence through immune modulation. Therefore, the clinical significance of the immunosuppressive effects of RBC transfusions have not been clearly established.

In Canada, the cost of administering allogeneic RBCs is not passed on to patients directly and, as a result, have no impact on bedside transfusion decisions. However, information regarding costs may be extremely relevant when comparing allogeneic cells to alternative strategies such as autologous blood programs, use of other O_2 carriers or pharmaceutical interventions. We identified 7 studies[79,80,223–227] that attempted to establish the cost of allogeneic RBC transfusions. In a Canadian study,[224] data from a 13-centre clinical trial evaluating erythropoeitin were used to determine the cost of allogeneic RBC units; $210/unit was

estimated using a hospital perspective,[80] data collected from 8 Canadian hospitals and 6 blood centres were used to establish the unit cost at $210 for in-patient allogeneic RBC transfusions and $280 for outpatient transfusions. In this same study, 59% ($124) of the cost was related to blood banking, personnel and hospital equipment; 31% ($64) was incurred in the collection process.

A multicentre study in the United States estimated

Table 6: Clinical studies evaluating quality of life and symptoms potentially associated with anemia

Study	Level of evidence	No. of patients	Study design	Study population	Blinding	Interventions	Outcomes	Comments
Quality of life								
Henry et al[24] (1992)	I	255/297*	RCT	AIDS and AZT	Double	Intravenous EPO *(n = 102)* v. placebo *(n = 130)*	- 3.9% ($p = 0.0002$) increase in Hct with EPO - Decrease in transfusions from 5.2 to 3.2 U/patient ($p = 0.0061$) - Improved energy and activity levels	Large number of withdrawals from quality of life assessment.
Case et al[25] (1993)	I	153/157*	RCT	Cancer and chemotherapy	Double	Intravenous EPO *(n = 79)* v. placebo *(n = 74)*	- Increased Hct with EPO ($p = 0.0001$) - Improved energy level and ability to perform daily tasks - No improvement in quality of life ($p = 0.086$)	Significant dropout rate for quality of life assessment. A number of different cancer types represented.
Eschbach et al[23] (1989)	IV	333	Prospective study	Hemodialysis	None	Intravenous EPO	- Increase in Hct from baseline (24% to 34%) - Increased energy (26% to 48%) ($p = 0.06$) - Increased overall quality of life	No control group. Limited description of quality of life.
Canadian Erythropoeitin Study Group[22] (1990)	I	118	RCT	Hemodialysis	Double	Placebo *(n = 110)* v. EPO to maintain [Hb] of 95–110 g/L *(n = 40)* v. EPO to maintain [Hb] of 115–130 g/L *(n = 38)*	- EPO groups had improved scores for fatigue, physical symptoms, relationships and depression - No improvement on 6-minute walk test and psychosocial scores	Significant improvement in self-reported symptoms that appear to correlate with increased [Hb]
Evans et al[21] (1990)	IV	300	Prospective study	Hemodialysis	None	Intravenous EPO 150–300 U/kg 3 times/week	- Compared with baseline, more patients free from physical limitations (27% v. 47%, $p < 0.001$) - Improved energy - Relief from several self-reported symptoms	No control group. Estimates of improvement may be exaggerated. No [Hb] reported.
Deniston et al[196] (1990)	IV	91	Prospective study	Hemodialysis	None	Intravenous EPO	- Improved overall quality of life - Improved energy level	[Hb] not reported. Controls not adequate.
Symptoms								
Elwood et al[26] (1969)	I	91/111*	RCT	Women with iron deficiency anemia	Single	Oral iron therapy *(n = 49)* v. placebo *(n = 41)*	- No improvement in symptoms (irritability, palpitations, dizziness, breathlessness, fatigue, headache) - No clear relation between [Hb] and severity of symptoms	High baseline [Hb] 106 g/L. Significant number of withdrawals
Elwood and Hughes[27] (1970)	II	47/53*	RCT	Anemia (female)	Single	Oral iron therapy *(n = 26)* v. placebo *(n = 21)*	- No significant difference in psychomotor function (concentration, short-term memory, decision-making, dexterity) or anemic symptoms	Small sample size, so only able to exclude large treatment effects. Limited reporting of [Hb]; only 14 of 26 responded to iron.

Note: AZT = zidoanidine; AIDS = acquired immunodeficiency syndrome; EPO = erythropoetin (doses ranged from 100 to 300 U/kg, 3 times/week); Hct = hematocrit.
*Number of patients evaluated/Number randomized).

comparable costs for an allogeneic RBC unit ($155 [US]). However, the average cost to society in the United States was estimated at $458 [US]. This dollar value included indirect costs such as lost productivity, decreased psychological well-being and travel expenses. A study comparing the cost-effectiveness of allogeneic RBCs with leukocyte-depleted products found the latter to be more cost-effective per patient treated[225] because of decreased length of stay and associated costs ($7867 v. $12 347 [US], $p < 0.01$). Future studies may establish the cost-effectiveness of various approaches to the administration of RBCs as well as alternative interventions.

Finally, when making bedside transfusion decisions, one should also consider possible alternatives to RBC transfusions. All benefits, risks, harms and costs of new therapies should be compared to the best available therapy: allogeneic RBC transfusion. Although the use of autologous RBCs and erythropoeitin may decrease exposure to allogeneic RBCs, these alternatives have not been convincingly demonstrated to result in an overall benefit to patients. Future studies may help elucidate the optimal role of alternatives.

In summary, significant limitations are identified in the transfusion literature evaluating various strategies. Published clinical studies do not provide conclusive evidence supporting a specific approach to allogeneic RBC transfusions. Thus, clinical practice guidelines for the use of RBCs must still rely heavily on expert opinion.

What patient characteristics or diseases increase the risk of adverse outcomes following anemia?

Guidelines[3,4,155] and reviews[1,5,228] have indicated that anemia is less well tolerated in older patients, in the severely ill and in patients with coronary, cerebrovascular or respiratory disease. However, clinical evidence confirming that these factors are independently associated with an increased risk of adverse outcome is lacking. One small case–control study[189] following high-risk vascular surgery suggests an increase in postoperative cardiac events with increasing severity of anemia. Two large cohort studies of perioperative[229] and critically ill patients[230] have reported increasing degrees of anemia associated with a disproportionate increase in mortality rate in the subgroup of patients with cardiac disease. In 1958, in Jehovah's witness patients[229] adjusted odds of death increased from 2.3 (95% CI 1.4 to 4.0) to 12.3 (95% CI 2.5 to 62.1) as preoperative [Hb] declined from 100–109 g/L to 60–69 g/L in patients with cardiac disease. There was no significant increase in mortality in noncardiac patients with comparable levels of anemia. Critically ill patients[230] with cardiac disease also tended to have higher mortality when [Hb] < 95 g/L (55% versus 42%, $p = 0.09$) compared with anemic patients with other diagnoses. Patients with anemia, a high APACHE II score (>20) and a cardiac diagnosis had a significantly lower mortality rate when given 1–3 or 4–6 units of allogeneic RBCs: 55% (no transfusion) v. 35% (1–3 units) or 32% (4–6 units), $p = 0.01$). Although both cohort studies were retrospective and may not have controlled for a number of important confounders, the evidence suggested that anemia increased the risk of death in patients with significant cardiac disease.

Severity of illness also appears to be a risk factor in the critically ill.[185,230] Two retrospective studies report that degree of blood loss contributes to perioperative

Table 7: Randomized, controlled clinical trials evaluating the risk of postoperative infection

Study	No. patients	Study population	Intervention	Rate of infection	Comments
Houbiers et al[28] (1997)	697	Colorectal surgery	Leukocyte-depleted (fresh) v. standard	42% v. 36% (not significant)	Large multicentre trial. Cancer recurrence is primary outcome.
Jensen et al[29] (1996)	589	Colorectal surgery	Leukocyte-depleted (stored) v. standard	0% v. 18.3%	High rates of postoperative infection. Very significant effect.
van de Watering et al[32] (1996)	914	Cardiac surgery	Leukocyte-depleted (fresh) v. leukocyte-depleted (stored) v. standard	16.7% v. 17.7% v. 22.7% ($p < 0.01$)	No difference in mortality overall, but decrease in leukocyte-depleted v. standard
Heiss et al[35] (1993)	120	Colorectal surgery	Autologous v. standard	12% v. 27% ($p < 0.05$)	No increase in postoperative infection in autologous v. untransfused.
Busch et al[34] (1993)	475	Colorectal surgery	Autologous v. standard	25% v. 27%	Large multicentre trial. Cancer recurrence is primary outcome.
Jensen et al[33] (1992)	197	Colorectal surgery	Leukocyte-depleted whole blood v. whole blood	2% v. 23% ($p < 0.01$)	Natural killer cell function reduced.

Source: Adapted from Blajchman.[221]

mortality.[185,230] However, no studies have examined the independent contribution of age, cerebrovascular disease and respiratory disease to increased mortality risk in anemic patients. This relation may well be complex given that age and cerebrovascular disease are risk factors associated with coronary artery disease. Smoking-related respiratory diseases may have similar associations with cardiac disease. Therefore, the association between anemia and increased rates of adverse outcomes in these patients can best be described as speculative, at this time.

Conclusion

We were able to draw several inferences from the literature. A significant variation in allogeneic RBC transfusion practice has been reported in a number of studies and a variety of patient populations. Despite this, few studies attempt to explain or minimize excessive practice variation. Similarly, studies evaluating the appropriateness of RBC transfusions reveal that a proportion may be unnecessary. Only 2 randomized, controlled trials, 1 evaluating a teaching program and another the use of an intra-operative transfusion algorithm, demonstrated that specific interventions may be employed to maximize appropriateness.

One of the most important questions facing the practitioner is whether there is an optimal [Hb] at which to maintain most anemic patients or certain patient groups. Six RCTs evaluated various [Hb] transfusion thresholds. A single level-I study demonstrated that there were no differences in the frequency of sickle-cell crises in patients treated with a conservative transfusion strategy compared with more liberal use of allogeneic RBCs. The 5 other small RCTs did not provide conclusive evidence to support an optimal [Hb] or approach to the administration of RBCs. Therefore, clinical practice guidelines addressing optimal [Hb] at which to maintain patients or administer RBCs would not be based on well-controlled clinical trials but rather on weaker grades of evidence as well as expert opinion. We suggest that level-I RCTs comparing transfusion strategies in various patient populations be conducted to develop high-grade evidence-based recommendations.

Clinicians wish to know if certain patients are at increased risk of suffering adverse outcomes following the development of anemia. Two clinical studies suggested that complications from anemia are greatest in patients with cardiac disease. Associations between anemia and adverse outcomes, as well as modification in the degree of risk in patients with other potential risk factors such as increased age and disease severity, respiratory and cerebrovascular disease, have not been clearly established using rigorous study designs.

A number of RCTs have also evaluated the effect of [Hb] on health-related quality of life and symptoms such as dyspnea, fatigue and exercise capacity using erythropoeitin and iron as means of increasing [Hb]. Most erythropoeitin studies suggested improvements in many of these subjective outcomes whereas studies using iron therapy did not find significant differences. Unfortunately, we found no level-I studies comparing patients who were maintained at low [Hb] with patients transfused to higher [Hb]. Recently, well-conducted clinical trials failed to demonstrate that observed increased rates of postoperative infections were more frequent in patients administered standard allogeneic RBCs compared with untransfused patients or patients receiving leukocyte-depleted or autologous RBC products. Thus, there is still no consensus on whether early immunosuppressive effects of allogeneic RBCs may have clinically important consequences.

Despite the many deficiencies in the clinical transfusion literature, there was a substantial body of evidence of practice variation and unnecessary transfusion. The clinical studies identified did not indicate an optimal [Hb], but did suggest that patients with cardiac disease were at increased risk.

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