Chapter 4: Red cell transfusion to treat anemia in CKD

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USE OF RED CELL TRANSFUSION IN CHRONIC ANEMIA

Repeated transfusions or use of an erythropoiesis-stimulating agent (ESA) are treatment options for chronic anemia in CKD. The choice between these depends on their relative benefits and harms, which vary among patients. For example, patients with a previous stroke have the greatest absolute risk of ESA-related stroke,[127] whereas multiparous women have the highest risk of allosensitization with transfusion.[190,191] Although the clinical importance of allosensitization is disputed, it may delay or reduce the possibility of future kidney transplantation.

4.1.1: When managing chronic anemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (*1B*)

4.1.2: In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (*1C*)

4.1.3: When managing chronic anemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (*2C*):

- **ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)**
- **The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)**

4.1.4: We suggest that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia. (*2C*)

RATIONALE

As with any treatment, the use of red cell transfusions should be considered in terms of the balance of benefit and harms. The primary benefit is in maintaining sufficient oxygen-carrying capacity and improvement in anemia-related symptoms.[192] The harms are summarized in Tables 5 and 6 and discussed further below. This balance must also be considered alongside the balance between the benefits and harms of ESA therapy which is an alternative treatment for the anemia of CKD. The benefits and harms of ESA therapy are discussed in detail in Chapter 3, but, in summary, the benefits include improvement in anemia-related symptoms and reduced need for transfusion, and the most important harms are increased risk of stroke, thromboembolic events, and cancer progression or recurrence. When choosing between these two treatments for anemia in an individual, patient characteristics which influence the balance between benefits and harms for each treatment should be considered. These include history of stroke and previous or current cancer which place patients receiving ESA therapy at much higher absolute risk of these two problems. Conversely, patients potentially eligible for kidney transplantation have the greatest potential harm from transfusion, in terms of allosensitization,[191,193,194] although the clinical importance of allosensitization is disputed. Previously transplanted patients and multiparous women seem to have the greatest absolute risk of allosensitization.[190,191]

A related issue is when should the decision to treat a patient with either an ESA or a transfusion be made? This decision is subtly different for the two types of treatment as ESAs may be used to *avoid* transfusion and therefore before the need for transfusion has arisen i.e., in a *prophylactic* sense. Furthermore, the magnitude of the potential harms of transfusion (e.g., from infection) and some of the benefits from ESAs (e.g., transfusion avoidance) is dependent on the threshold for transfusion. If that threshold is high (i.e., transfusion is reserved until symptoms become severe or the Hb reaches a very low level) the risks related to transfusion will be low and the benefit of ESA therapy in avoiding transfusions will be small. Unfortunately, there is no consensus about when transfusion is indicated although we do know that the rate of transfusion increases markedly when the Hb falls below 10 g/dl (100 g/l);[122,127] whether that simply reflects practice-patterns or represents clear clinical need is uncertain. The following trials give examples of transfusion rates in CKD 5D and CKD ND patients. The trial conducted by the Canadian Erythropoietin Study Group, published in 1990, enrolled 118 CKD 5HD patients Hb <9.0 g/dl (<90 g/l), 49 (42%) of whom were described as 'transfusion-dependent'.[122] The patients averaged approximately 7 transfusions each in the previous 12 months. These patients were randomized, equally, to 6 months treatment with placebo, erythropoietin with a target Hb 9.5–11.0 g/dl (95–110 g/l), or erythropoietin with a target Hb 11.5–13.0 g/dl (115–130 g/l). After 8 weeks, 23 patients in the placebo group received a blood-transfusion, compared with one in each of the two erythropoietin groups (for a gastrointestinal hemorrhage and following surgery). More recently, in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), published in 2009, 4038 patients with diabetes, CKD ND and anemia (Hb ≤ 11.0 g/dl [≤ 110 g/l]), were randomized, equally, to darbepoetin-alfa with target Hb 13 g/dl (130 g/l) or to placebo, with 'rescue' darbepoetin-alfa when Hb fell below 9.0 g/dl (90 g/l).[127] Over a median follow-up of 29 months, 297/2012 (15%) patients randomized to

Table 5 | Estimated risk associated with blood transfusions per unit transfused

Adverse event	Estimated risk*
Immunological	
Fever/allergic reactions	1 in 100–200[a,b]
Hemolytic reaction	1 in 6000[b]
Transfusion-related acute lung injury (TRALI)	1 in 12,350[a]
Anaphylaxis	1 in 50,000[b]
Fatal hemolysis	1 in 1,250,000[a]
Graft versus host disease (GVHD)	Rare
Other	
Mistransfusion	1 in 14,000–19,000[c]

*United States data.
[a]Data from Carson JL *et al.*[212]
[b]Data from Klein.[213]
[c]Data from Klein HG *et al.*[214]

Table 6 | Estimated risk of transfusion-related infections per unit transfused

Potential transfusion-related risks	Estimated risk*
Hepatitis B	1 in 282,000–1 in 357,000[a]
West Nile virus	1 in 350,000[b]
Death from bacterial sepsis	1 in 1,000,000[b]
Hepatitis C	1 in 1,149,000[a]
Human immunodeficiency virus (HIV)	1 in 1,467,000[a]

*United States data.
[a]Data from Carson JL *et al.*[212]
[b]Data from Rawn J.[215]

darbepoetin-alfa and 496/2026 (25%) assigned to placebo received red cell transfusions (HR 0.56, 95% CI 0.49–0.65, $P<0.001$).

We suggest that the decision to transfuse in the patient with non-acute anemia related to CKD should not be based upon any arbitrary Hb threshold and should, instead, be determined by the occurrence of symptoms and signs caused by anemia. We recognize that symptoms such as dyspnea and fatigue are non-specific, and that anemia-related symptoms may occur at different Hb levels in different patients.

Risks of blood transfusion

Risks associated with blood transfusion include transfusion errors, volume overload, hyperkalemia, citrate toxicity (leading to metabolic alkalosis and hypocalcemia), hypothermia, coagulopathy, immunologically-mediated transfusion reactions, including transfusion-related acute lung injury (TRALI), and iron overload, all of which are uncommon (Table 5).[190,195–207] Transmission of infections, although rare, is a major concern and this risk varies between countries (Table 6).[208–211] These complications are reviewed extensively elsewhere. The importance of human leukocyte antigen (HLA) sensitization is disputed and discussed in more detail below.

HLA sensitization. The risk of sensitization after blood transfusion has changed over time probably, at least in part, due to changes in blood transfusion practices and the use of more precise methods to measure allosensitization.

In the early 1980s, Opelz *et al.* examined the risk of sensitization in 737 CKD 5HD patients (Figures 3A and 3B), of whom 331 were followed prospectively (Figure 3C).[190] Approximately 90% of all transfusions were given in the form of 'packed cells' and antibodies were measured by the lymphocyte cytotoxicity test. Overall, 28% of patients followed prospectively developed HLA antibodies. Of these, 18% developed reactivity to 10–50% of the panel, 7% to 50–90%, and $<3\%$ to $>90\%$ of the panel after up to 20 transfusions (Figure 3C). Among men, 90% remained 'unresponsive' ($<10\%$ antibody reactivity against the panel) and 10% developed reactivity to 10–50% of the panel (Figure 3C). In contrast, after 10 transfusions, only 60% of the women were 'unresponsive,' 11% demonstrated 10–50% reactivity, 23% 51–90% reactivity, and 6% $>90\%$ reactivity (Figure 3C). These data suggested that the main drivers of HLA sensitization following red cell transfusion are previous pregnancies and previous transplantation. The data also suggested that men have a much lower risk of HLA sensitization following transfusion than women, and women with multiple pregnancies have a much greater risk of HLA sensitization than nulliparous women. However, more recent data from the US Renal Data System (USRDS) 2010 Annual Report,[191] have challenged this assumption, suggesting that males receiving previous blood transfusions may also be at increased risk.

Studies performed in the last two decades showed that the risk of sensitization with blood transfusion is apparently lower than previously reported, with an overall response rate ranging from 2 to 21%.[216–218] A possible, albeit controversial, explanation for this lower sensitization rate is that red cell transfusions in recent years are less immunogenic because they contain fewer leukocytes due to widespread use of blood filters.

Other tentative conclusions from previous studies include the following: a) washed-red cells do not appear to be less immunogenic than non-washed red cells;[190] b) no consistent reduction in sensitization has been demonstrated with donor-specific[217] and HLA-DR matched transfusions;[219] c) higher numbers of blood transfusions have been associated with an increased risk of sensitization in some studies[220,221] but not in others.[190,222]

However, more recent data from the USRDS indicates that risk of sensitization with blood transfusions is substantial. For example, compared with patients who have never received a blood transfusion, patients who received transfusions have an odds ratio of having panel reactive antibody (PRA) $>80\%$ of 2.38.[191] Interestingly, in this analysis the risk of being highly sensitized at the time of transplantation was higher for men than for women.

Effect of leukocyte-reduced blood transfusions on sensitization. Although, leukocytes may be a contributor to, if not the cause of, a number of adverse consequences of blood transfusion, including immunologically-mediated effects,

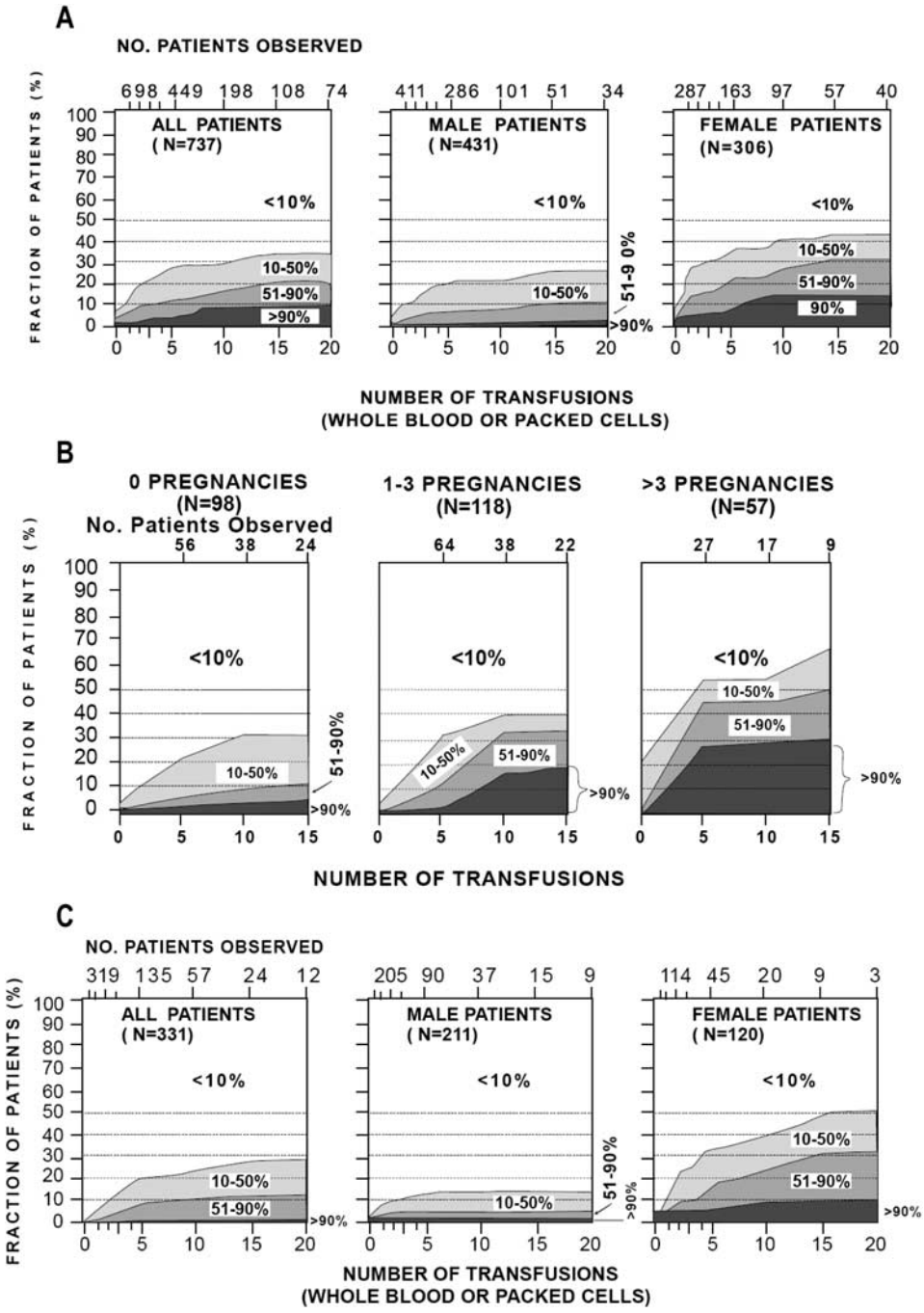

Figure 3 | Lymphocytotoxic antibody reactivity against random donor test panel in relation to the number of blood transfusions. Fractions of patients reacting against $<10\%$, 10 to 50%, 51 to 90% and $>90\%$ of the panel donors are plotted. All 737 patients were on chronic hemodialysis, waiting for a first kidney transplant. Numbers of patients after 2, 5, 10, 15, and 20 transfusions are indicated at top of graphs. (**A**) Male and female patients. (**B**) Females patients separated by the number of previous pregnancies. (**C**) Lymphocytotoxic antibodies in patients who were studied prospectively throughout the course of treatment. Reprinted from Opelz G, Graver B, Mickey MR *et al*. Lymphocytotoxic antibody responses to transfusions in potential kidney transplant recipients. *Transplantation* 1981; 32(3): 177–183 (ref. 190) with permission from Lippincott Williams & Wilkins; accessed http://journals.lww.com/transplantjournal/Abstract/1981/09000/Lymphocytotoxic_Antibody_Responses_to_Transfusions.2.aspx

infectious disease transmission, and reperfusion injury, leukoreduction of blood products does not decrease sensitization in previously transplanted or in potential future kidney transplant candidates.[223–225] One recent study reported that male patients awaiting their first organ transplant had a fourfold increased risk of developing HLA antibody if they had been previously transfused when compared with those who did not have a history of a transfusion.[226] Thus,

Table 7 | Indications for blood transfusions

Indication	Comments
When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable myocardial ischemia)	• Red cell transfusion in patients with acute hemorrhage is indicated in the following situations: a) rapid acute hemorrhage without immediate control of bleeding; b) estimated blood loss >30–40% of blood volume (1500–2000 ml) with symptoms of severe blood loss; c) estimated blood loss <25–30% blood volume with no evidence of uncontrolled hemorrhage, if signs of hypovolemia recur despite colloid/crystalloid resuscitation; d) in patients with co-morbid factors, transfusions may be necessary with lesser degrees of blood loss.[234] • Studies evaluating the importance of anemia and the role of transfusion in the setting of an acute coronary syndrome (i.e., unstable angina, myocardial infarction) have reached differing conclusions. • The American College of Cardiology/American Heart Association and American College of Chest Physicians guidelines do not make any recommendations concerning the potential benefit or risk of blood transfusion in the setting of an acute coronary syndrome.[235,236] However, in a review of clinical trials of patients with a non-ST elevation acute coronary syndrome, the risk of cardiovascular mortality, nonfatal myocardial infarction, or recurrent ischemia at 30 days was significantly higher in patients with a Hb concentration below 11 g/dl (110 g/l) than those with a Hb ≥11 g/dl (≥110 g/l).[237] • Although anemia occurs frequently in patients with heart failure, limited data are available on treatment of anemia in this population. • Correction of anemia is not an evidence-based therapy in heart failure as noted in the 2006 Heart Failure Society of America guidelines, 2012 European Society of Cardiology (ESC) guidelines, and 2009 American College of Cardiology/American Heart Association guidelines.[238–240] • Therefore, the general indications for red cell transfusion apply to patients with heart failure; however, careful attention must be paid to volume status.
When rapid pre-operative Hb correction is required	• Criteria have been proposed for perioperative transfusions.[234] These are generally not recommended when the Hb is ≥10 g/dl (≥100 g/l) in otherwise healthy subjects, but should be given when the Hb is less than 7 g/dl (70 g/l). • When Hb concentration is less than 7 g/dl (70 g/l) and the patient is otherwise stable, 2 units of red cells should be transfused and the patient's clinical status and circulating Hb should be reassessed. • High-risk patients (>65 years and/or those with cardiovascular or respiratory disease) may tolerate anemia poorly, and may be transfused when Hb concentration is less than 8 g/dl (80 g/l). • For Hb concentration between 7 and 10 g/dl (70 and 100 g/l), the correct strategy is unclear.
When symptoms and signs related to anemia are present in patients in whom ESA therapy is ineffective (e.g., bone marrow failure, hemoglobinopathies, ESA resistance)	• Patients with chronic anemia (e.g., bone marrow failure syndromes) may be dependent upon red cell replacement over a period of months or years, which can lead to iron overload. • Approximately 200 mg of iron are delivered per unit of red cells; this iron is released when Hb from the transfused red cells is metabolized after red cell death. • Given the progressive loss of red cell viability which occurs during storage, the "freshest-available" units should be selected in order to maximize post-transfusion survival. • Hemosiderosis can produce organ damage when the total iron delivered approaches 15 to 20 grams, the amount of iron in 75 to 100 units of red cells. • The issue of red cell transfusion in patients with acquired or congenital hemolytic anemia is more complex.
When symptoms and signs related to anemia are present in patients in whom the risks of ESA therapy may outweigh the benefits	• ESAs should be used with great caution, if at all, in CKD patients with active malignancy, a history of malignancy, or prior history of stroke.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

transfusion in the post-leukodepletion era still continues to pose a significant risk of sensitization. A possible reason for this finding is that the number of HLA molecules contributed by the red cells is comparable to that of leukocytes.[227]

Association between sensitization and delay in organ transplantation. According to USRDS data reported in 2010, the mean wait-time to transplant for patients listed between 1991 and 2008 was an average of 2 months longer for transfused than non-transfused patients in the United States.[191] Increased PRA titers, whether due to blood transfusions or other factors, were associated with a longer wait to find a compatible donor and may have completely precluded transplantation in some patients. Non-sensitized patients (0% PRA at the time of listing) had the shortest wait-time (median of 2.5 years in 2005) while those with a PRA of 1–19% and 20–79% had median wait-times of 2.9 and 4.3 years, respectively. Highly sensitized patients (≥80% PRA) waited the longest and in these patients a median wait-time

could not be calculated for patients listed in 2005. As a result of the delay in finding compatible donors in patients with PRA $\geq$80%, the percentage of these patients increased from 7.5% at listing to 13.3% five years after listing.

Not being transplanted, or having to wait longer for transplantation, is associated with lower survival.[228,229] Receiving a transfusion while on the transplant wait list is associated with a nearly 5-fold higher risk of dying while on

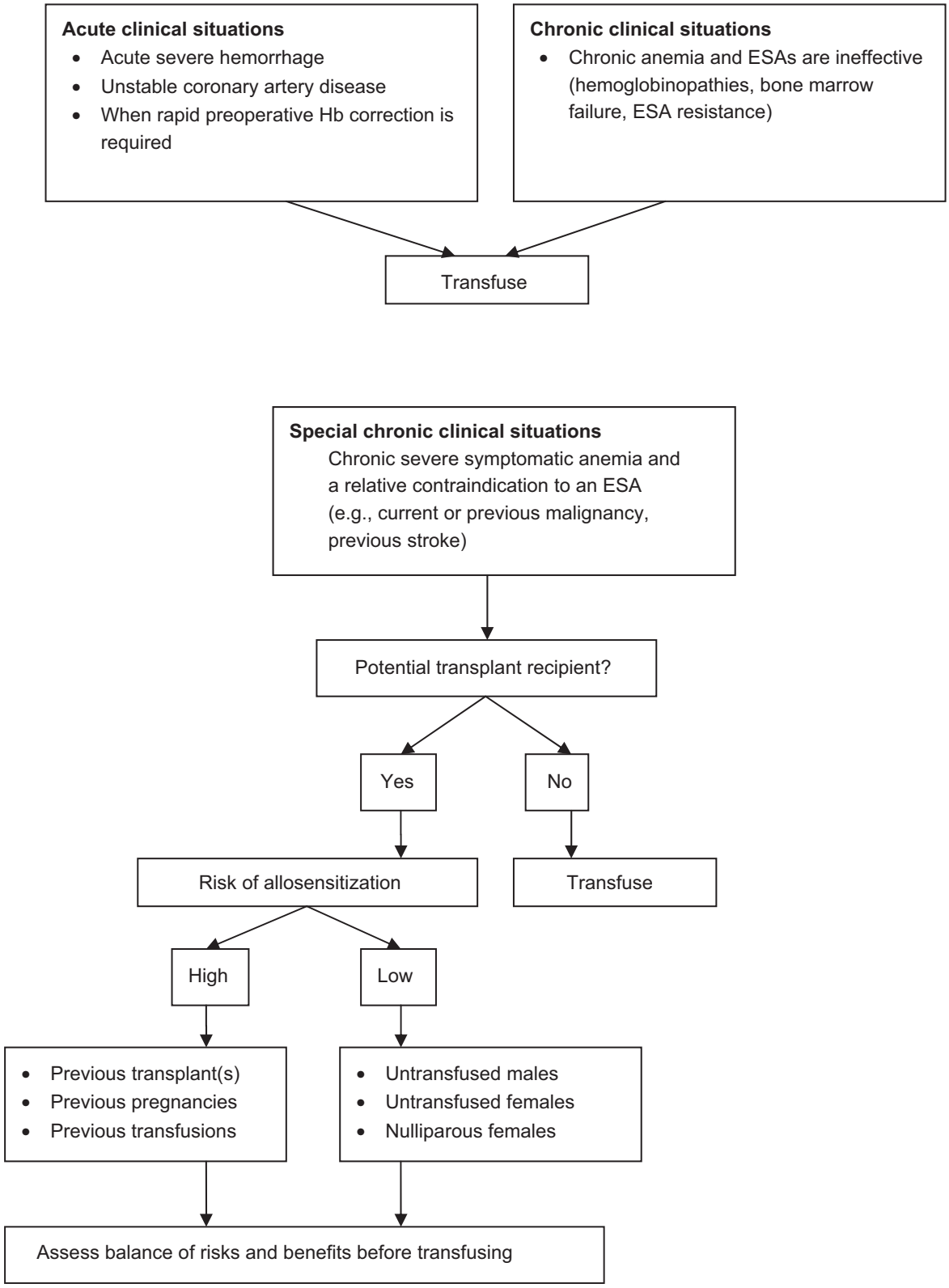

Figure 4 | Algorithms for red cell transfusion use in CKD patients. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

the wait list in the first five years, and an 11% reduction in the likelihood of receiving a transplant within the first five years.[191,230] In transplanted patients, the presence of preformed HLA antibodies is associated with an increased risk of early and late graft loss.[193,194,231,232] Recent data also suggest that pre-existing donor-specific HLA antibodies identified by a Luminex single-antigen assay at the time of transplantation are associated with a higher incidence of antibody-mediated rejection and inferior graft survival.[233]

URGENT TREATMENT OF ANEMIA

4.2: In certain acute clinical situations, we suggest patients are transfused when the benefits of red cell transfusions outweigh the risks; these include (*2C*):

- **When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)**
- **When rapid pre-operative Hb correction is required**

RATIONALE

In certain urgent clinical situations, red cell transfusion may be needed for the immediate correction of anemia. These include acute severe hemorrhage and other clinical problems caused by, or exacerbated by, anemia, such as acute myocardial ischemia. When urgent surgery is required, transfusion may also be given to achieve rapid preoperative correction of Hb. The Hb threshold for transfusion in this situation is uncertain but we suggest that this treatment be considered if the Hb is <7 g/dl (<70 g/l).

Table 7 and Figure 4 summarize the approaches to the use of red cell transfusions in patients with CKD.

RESEARCH RECOMMENDATIONS

There is a lack of randomized controlled trials on the use of blood transfusions as a primary intervention in patients with anemia and CKD. Given the logistical difficulties in conducting such trials, it is likely that observational data will continue to predominate in this therapeutic area.

Future research should include:

- Prospective observational data collection on the use of red cell transfusions in CKD patients, particularly dialysis patients, including the reason(s) for transfusion, intent to list for future kidney transplantation, likelihood of receiving a kidney transplant, and graft outcomes.
- Prospective observational evaluation of the impact of red cell transfusions on the level of HLA sensitization.
- Given a striking disparity in the use of blood transfusions between the US and Europe, Canada and Australia in the TREAT study, and between the US and Europe in the Phase 3 peginesatide clinical trial program, further research is needed to ascertain the 'drivers' for transfusion in CKD patients. Is this related to practice patterns or a real higher clinical need for transfusions in the US?

DISCLAIMER