# Recommendations for the transfusion of red blood cells

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## Introduction

The transfusion of red cell concentrates (RCC) is indicated in order to achieve a fast increase in the supply of oxygen to the tissues, when the concentration of haemoglobin (Hb) is low and/or the oxygen carrying capacity is reduced, in the presence of inadequate physiological mechanisms of compensation (table I)[1-14].

**Tissue oxygenation depends on various factors**:
- the concentration of Hb;
- the saturation of Hb, which, in turn, depends on the $O_2$ tension and the affinity of the Hb for $O_2$;
- the $O_2$ requirement, that is, the volume of oxygen needed by the tissues to carry out their aerobic function.

**Table I** –Mechanisms of adaptation to anaemia

| |
|---|
| Increased cardiac output |
| Increased coronary artery blood flow |
| Redistribution of blood flow |
| Increased oxygen extraction |
| Increase of red blood cell 2,3-diphosphoglycerate |

**Clinical factors that affect the physiological mechanisms of adaptation to anaemia[5-8,15-19]:**
- a reduced increase in cardiac output: hypovolaemia, coronary artery disease, disorders of heart valves, congestive heart disease, negative inotropic drugs;
- decreased capacity to increase the extraction of $O_2$: acute respiratory distress syndrome (ARDS), sepsis, systemic inflammatory response syndrome (SIRS), traumatic ischaemia-reperfusion damage syndrome;
- altered gas exchange: chronic obstructive pulmonary disease (COPD), ARDS;
- increased consumption of $O_2$: fever, pain, stress, sepsis, SIRS, hyperventilation syndromes.

When there is an indication to correct anaemia, but the situation is not urgent, strategies other than transfusion are preferred, such as the use of haematopoietic drugs (iron, vitamin $B_{12}$, folic acid, recombinant erythropoietin)[5-8,20].

In order to reduce perioperative bleeding, it is important to suspend treatment with platelet anti-aggregants, adapt/neutralise anticoagulant therapy and use drugs such as antifibrinolytics and desmopressin[9,20-23].

Autotransfusion, carried out according to the criteria set out in the appropriate pre-operative request schemes (maximum surgical blood order schedule - MSBOS), and surgical and anaesthetic techniques to limit blood loss are useful strategies for decreasing the use of homologous blood *(Grade of recommendation: 1C+)*[5,6,13,14,20-24].

## Parameters for evaluating anaemia

The only indication for the transfusion of RCC is to correct or prevent tissue hypoxia; thus, the parameter "of choice" for making decisions should be intracellular $pO_2$[17,25,26]. This parameter is not, however, usable for clinical purposes and it is, therefore, necessary to fall back on "surrogate" parameters, such as Hb and the haematocrit (Htc). The indication for and the degree of urgency of RCC transfusions cannot, however, be defined only on the basis of the values of Hb or the Htc[3-12,14,27], but must be based on a complete evaluation of the patient's clinical condition (table II) and the possible presence of mechanisms compensating for the anaemia (table I).


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**Table II** – Clinical parameters to evaluate when considering a transfusion

| | |
|---|---|
| Age | Cardiac function |
| Signs and symptoms of anaemia | Lung function |
| Speed of blood loss | Ischaemic heart disease |
| Volume of blood loss | Pharmacological treatments |

## The physiology of red blood cells

The normal daily production of red blood cells (RBC) in a healthy adult is about 0.25 mL/kg and the average lifespan of the cells is about 120 days, whereas that of transfused RBCs is about 50-60 days and can be significantly shorter in the presence of factors reducing their survival.

The storage of RCCs leads to a series of metabolic, biochemical and molecular changes, defined globally as the storage lesion; the extent of these changes is related to the duration of the period of storage[28-30].

Depletion of 2,3-diphosphoglycerate (2,3-DPG) occurs within a few days of the start of storage and is complete within 1 or 2 weeks.

This alteration is reversible: 50% of the 2,3-DPG is restored by 8 hours after starting the transfusion, while 24 – 72 hours are necessary for complete recovery. This can be clinically relevant in patients who require massive transfusions[31-32].

## Available forms of RCCs

The following forms of RCCs are available for the treatment of anaemia (see appendix B)[33-35]:

1. RBC concentrates.
2. RBC concentrates deprived of the buffy coat.
3. RBC concentrates with additive solutions.
4. RBC concentrates deprived of the buffy coat and resuspended in additive solutions.
5. Washed RBC.
6. Leucodepleted RBC.
7. Frozen RBC.
8. Apheretic RBC.
9. Irradiated RBC.

## Transfusion yield

As a rough guide, in the adult, one unit of RCC increases the Hb concentration by 1 g/dL and the Htc by about 3%[5-10,36-39]. Table III reports the increases in Hb and Htc according to the patient's weight and blood volume.

In children, the transfusion of 5 mL/kg increases the Hb concentration by about 1 g/dL.

In the case of a lower than expected transfusion yield, conditions causing the loss, sequestration or destruction of RBCs should be looked for. Such conditions include:

- occult bleeding;
- repeated blood sampling (particularly in children);
- fever;
- hypersplenism;
- primary and secondary immunological causes;
- mechanical or other type of haemolysis.

## Indications for the transfusion of RCC

The criteria for blood-group compatibility for the transfusion of RBC are reported in table IV .

**Table III –** Mean increase in Hb and Htc 24 h after the administration of one unit of red cell concentrate

| | MALES (Increase) | | | FEMALES (Increase) | | |
|---|---|---|---|---|---|---|
| **Weight (kg)** | **Volaemia (mL)** | **Hb (g/dL)** | **Htc (%)** | **Volaemia (mL)** | **Hb (g/dL)** | **Htc (%)** |
| 20 | 1,350 | 2.3 | 6.6 | 1,260 | 2.5 | 7.0 |
| 30 | 2,025 | 1.6 | 4.6 | 1,890 | 1.7 | 5.0 |
| 40 | 2,700 | 1.2 | 3.6 | 2,520 | 1.3 | 3.9 |
| 50 | 3,375 | 1.0 | 3.0 | 3,150 | 1.1 | 3.2 |
| 60 | 4,050 | 0.9 | 2.6 | 3,780 | 1.0 | 2.7 |
| 70 | 4,725 | 0.8 | 2.2 | 4,410 | 0.8 | 2.3 |
| 80 | 5,400 | 0.7 | 2.0 | 5,040 | 0.7 | 2.0 |
| 90 | 6,075 | 0.6 | 1.7 | 5,670 | 0.6 | 1.8 |
| 100 | 6,750 | 0.5 | 1.5 | 6,300 | 0.5 | 1.6 |



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**Table IV –** Transfusion therapy with RBC: selection of the ABO phenotype of units to transfuse

| ABO phenotype of the recipient | ABO phenotype of units to transfuse (in order of preference) |
|---|---|
| O | O |
| A | A, O |
| B | B, O |
| AB | AB, A, B, O |

## 1. Transfusion of RCCs in acute anaemia

The decision to transfuse RBCs is based on the concentration of Hb, the amount of blood loss and the clinical condition of the patient[1-12,14,25,40-49].

The main therapeutic strategy in the treatment of acute haemorrhage is to prevent or correct hypovolaemic shock. In order to ensure tissue oxygenation it is essential to restore circulatory volume by infusing crystalloids/colloids in sufficient amounts to maintain a satisfactory blood flow and blood pressure.

A loss of less than 15% of the blood volume does not normally produce symptoms nor does it require transfusion, unless there is pre-existing anaemia (table V) *(Grade of recommendation: 2C+)*[5-10,49].

When the loss of volume is between 15 and 30% a compensatory tachycardia develops and the transfusion of RCCs is indicated only in the presence of pre-existing anaemia or concomitant cardiac or pulmonary disease (table V) *(Grade of recommendation: 2C+)*[5-10,49].

Blood volume losses exceeding 30% can cause shock and when the volume loss is more than 40%, the shock is severe.

The probability of having to administer RCC transfusion therapy increases notably when the volume loss is between 30-40%, even though volume replacement alone may be sufficient in previously healthy subjects (table V) *(Grade of recommendation: 2C+)*[5-10,49].

Transfusion becomes a life-saving intervention when the blood volume loss is more than 40% (table V) *(Grade of recommendation: 2C+)*[5-10,49].

Subjects with Hb concentrations below 6 g/dL almost always require transfusion therapy. In stabilised patients with Hb values between 6 and 10 g/dL, the decision whether to transfuse is based on an evaluation of clinical status; patients with values above 10 g/dL rarely require transfusion *(Grade of recommendation: 1A)*[5-10,14,41-45,49].

It should also be remembered that patients with acute haemorrhage can have normal, or even high, Htc values until the plasma volume is restored; the clinical evaluation of the patient in this situation is, therefore, extremely important *(Grade of recommendation: 2C+)*[5-10,48,49].

Among patients in intensive care, no significant differences were found in 30-day mortality rates between those in whom 'restrictive' transfusion therapy was used and those in whom the transfusion therapy was applied 'liberally' (triggering Hb values between 7-8 g/dL and around 10 g/dL, respectively). There is evidence that a restrictive regime does not cause significant increases in mortality, cardiac morbidity or duration of hospitalisation. Patients with underlying cardiovascular disease represent a possible exception *(Grade of recommendation: 1C+)*[5-12,14,21,23,27,40-47,50-52].

**Table V –** Decisional criteria for transfusion in acute anaemia (GoR: grade of recommendation)

| Class of haemorrhage | Percentage reduction in blood volume | mL * | Indication for the transfusion of RCCs | GoR |
|---|---|---|---|---|
| Class I | < 15 % | < 750 | Not necessary, unless pre-existing anaemia | 2C+ |
| Class II | 15-30 % | 750-1,500 | Not necessary, unless pre-existing anaemia and/or cardiopulmonary disease | 2C+ |
| Class III | 30-40 % | 1,500-2,000 | Probably necessary | 2C+ |
| Class IV | > 40 % | > 2,000 | Necessary | 2C+ |

* In an adult weighing 70 kg with a circulatory volume of 5,000 mL.

## 2. Transfusion of RCCs in chronic anaemia

In chronic anaemia there are increases in the content of 2,3-DPG in the red blood cells, with a shift towards the right in the Hb dissociation curve, and in the cardiac output and respiratory rate. For these reasons, it is rarely necessary to transfuse patients with Hb values above 8 g/dL (Table VI) *(Grade of recommendation: 1A)*[5-12,14,27,43-46].

The aetiopathogenesis of this type of anaemia must always be determined in order to treat it, if possible, with therapy other than transfusion [haematinics in forms due to deficiency (iron, vitamin $B_{12}$, folates) and/or erythropoietin in chronic renal failure or myelodysplastic syndromes].

When there is a marked decrease in oxygenation because of abnormalities in cardiovascular or respiratory function, a Hb threshold above 8 g/dL can be considered as the trigger for transfusion treatment (Table VI) *(Grade of recommendation: 2C+)*[8,11,12].

In patients undergoing chemotherapy or radiotherapy, who cannot wait for the effect of treatment with erythropoietin or in whom this hormone cannot be used because of specific receptors for it on the malignant cells, a suggested transfusion threshold is a Hb concentration of 10 g/dL, to counteract the protective effect of hypoxia on the neoplasia and to improve the pharmacokinetics of some chemotherapeutic agents in conditions of anaemia (Table VI) *(Grade of recommendation: 2C+)*[53-66].

The transfusion threshold in thalassaemia is generally 9-9.5 g/dL of Hb, in order to guarantee a balance between inhibition of bone marrow erythropoiesis and iron overload from transfusion therapy (Table VI) *(Grade of recommendation: 2C+)*[8,10,67-70].

In sickle cell disease the fundamental indications for transfusion therapy with RBC are anaemia and vascular occlusion.

Transfusion therapy is not normally indicated in patients with Hb values > 7 g/dL *(Grade of recommendation: 2C+)*[8,10,67,71-82].

In the presence of vascular occlusion, the aim of transfusion therapy is to prevent or stop intravascular sickling by dilution or replacement of the pathological circulating RBCs with normal RBCs; sickle cell patients must be transfused with RCCs lacking Hb S. It is improbable that these patients develop vaso-occlusion when the percentage of Hb S is below 30-40%. Red cell exchange is indicated for planned major surgery, ocular surgery and to prevent or treat acute vaso-occlusive crises *(Grade of recommendation: 2C+)*[8,10,67,71-82].

In thrombocytopenic patients transfusion therapy with RCC is indicated to maintain the Htc around 30% and to reduce the risk of haemorrhage *(Grade of recommendation: 1C+)*[83-95].

## 3. Transfusion of RCC in surgery

Patients in good clinical condition and with Hb values ≥ 10 g/dL rarely require perioperative transfusions, while patients with Hb levels around 7 g/dL often do *(Grade of recommendation: 1C+)*[5-14,20-25,96-102].

However, all decisions concerning transfusions in the case of surgery must take into consideration other factors: the type of operation, the extent and speed of blood loss, the presence of concomitant clinical conditions (age of the patient, heart disease, respiratory disorders).

In all cases in which the use of allogeneic blood is predictable and/or necessary, it is suggested that the requested number of units of RCC does not exceed that of the MSBOS indication for that particular operation *(Grade of recommendation: 2C+)*[13,21-23].

As an initial reference, the indications from the *British Committee for Standards in Haematology Blood Transfusion Task Force* are proposed. These guidelines report the maximum acceptable request in standard operating conditions and in the presence of

**Table VI -** Decisional criteria for transfusion in chronic anaemia (GoR: grade of recommendation)

| Hb value | | GoR |
|---|---|---|
| Hb < 8 g/dL | After evaluation of the aetiopathogenesis and consideration of possible alternatives to transfusion | 1A |
| Hb 8-10 g/dL | Transfuse RBC when there is a marked decrease in oxygenation (abnormal cardiocirculatory or respiratory function) | 2C+ |
| | Patients undergoing chemo-radiotherapy or thrombocytopenic patients | 1C+ |
| Hb 9-9.5 g/dL | Thalassaemic patients | 2C+ |



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**Table VII –** Proposed Maximum Surgical Blood Order Schedule (MSBOS) for different operations.

| | |
|---|---|
| **General surgery** | |
| Cholecystectomy and exploration of the bile duct; abdominal wall repair; vagotomy | (*) T&S |
| Explorative laparotomy | 2 |
| Oesophagectomy | 4 |
| Laparotomic repair of hiatus hernia; gastrostomy and enterostomy; gastric resections | T&S |
| Total gastrectomy | 2 |
| Oesophagogastrectomy | 4 |
| Hepatic resections | 2 |
| Hepatectomy | 4 |
| Rectal resection via the abdominal-perineal route | 4 |
| Anterior resection of the rectum | 2 |
| Ileal resections | 4 |
| Resections of the colon, hemicolectomy, colectomy | 2 |
| Simple mastectomy; thyroidectomy; parathyroidectomy; liver biopsy; splenectomy | T&S |
| Excision of adrenal gland | 3 |
| Pancreatectomy | 4 |
| Kidney transplant; bone marrow harvest | 2 |
| **Thoracic surgery** | |
| Lung biopsy; mediastinoscopy; explorative thoracotomy | T&S |
| Pneumectomy; lobectomy; pleural decortication | 2 |
| **Cardiovascular surgery** | |
| Amputation of a leg; sympathectomy; femoral thromboendoarterectomy (TEA); carotid TEA | T&S |
| Aorto-femoral by-pass | 2 |
| Aorto-iliac by-pass | 4 |
| Abdominal aorta aneurysmectomy | 4 |
| Thoracic aorta aneurysmectomy | 6 |
| Saphenectomy; varicectomy | T&S |
| Valve replacements; aorto-coronary by-pass | 4 |
| **Neurosurgery** | |
| Pituitary gland surgery; laminectomy for lumbosacral hernia discs; shunts for hydrocephalus | T&S |
| Excision of meningioma | 2 |
| Excision of primary/secondary brain tumours | 2 |
| Chronic subdural haematoma; cranioplasty | T&S |
| Cerebral aneurysmectomy | 2 |
| **Urology** | |
| Transurethral resection of prostate (TURP); transurethral resection of bladder | T&S |
| Open adenomectomy of prostate | 2 |
| Radical prostatectomy | 4 |
| Cystectomy | 4 |
| Radical nephrectomy | 2 |
| Percutaneous pyelolithotomy | T&S |
| **Obstetrics/Gynaecology** | |
| Caesarean section; abdominal/vaginal hysterectomy | T&S |
| Laparo-hysterectomy with bilateral removal of adnexae | 4 |
| Pelviectomy | 6 |
| Asportation of a vesicular mole | 2 |
| **Orthopaedic surgery** | |
| Osteotomy/bone biopsy | T&S |
| Bone graft from iliac crest; spinal column arthrodesis | 2 |
| Hip, knee, shoulder, elbow prosthesis | 2 |
| Removal of hip synthesis systems, femoral nails | T&S |
| Hip prosthesis replacement | 4 |

**(*) T&S = Type and Screen** (*Type* = typing the red blood cells, with determination of ABO groups and Rh type; *Screen* = search for irregular red blood cell antibodies)

good transfusion practice (table VII).

It is to be hoped that the MSBOS in every health care structure is adapted to the local reality.

The MSBOS also serves as a guide for the indication for autotransfusion. Autotransfusion must be limited to cases of elective surgery for which the predicted transfusion requirements are at least two units of RCCs and for which there is enough time to collect the autologous units and allow haematopoietic recovery *(Grade of recommendation: 2C)*[13,21-23].

**4. Transfusion of RCCs in bone marrow transplantation**

The need for RCC transfusions in bone marrow transplantation (BMT) varies greatly from patient to patient. All patients who are candidates for BMT must be transfused only with leucocyte-depleted red cells that are preferably of the same group and phenotype *(Grade of recommendation: 2C+)*[103-108].

Blood components filtered with the latest generation filters, able to reduce the leucocyte content by 99.9%, are a valid alternative to cytomegalovirus (CMV)-negative blood components *(Grade of recommendation: 1C)*[105,106,108].

All patients undergoing allogeneic BMT should be transfused with irradiated blood components until the start of their conditioning chemotherapy or radiotherapy. This indication also continues until graft-versus-host disease (GvHD) prophylaxis is given: usually for 6 months or until the lymphocyte count exceeds 1,000/μL. Patients transplanted for combined immunodeficiency disease or with chronic GvHD, must receive irradiated blood components for a longer period, even for as long as 2 years *(Grade of recommendation: 2C+)*[105,109-111].

In transplanted patients, the aim of transfusion during the phase of thrombocytopenia is to maintain the Htc around 30% to reduce the risk of haemorrhage *(Grade of recommendation: 1C+)*[83-95].

The ABO/D group of RCCs to be transfused during allogeneic BMT must be contemporaneously compatible with the donor's and recipient's group *(Grade of recommendation: 1C+)*[104,107].

**5. Transfusion of RCCs in neonates**

Units of smaller volume (25-100 mL) can be prepared for children by fractionating a standard unit of RCCs into several aliquots; these aliquots can be transfused in succession, in this way reducing the number of donors to which the recipient is exposed[38].

RCCs used in the neonatal period must be leucodepleted, preferably at the time of collection (prestorage), but at any rate, within 72 hours of collection *(Grade of recommendation: 1C)*[38,67,112,113].

In order to prevent GvHD, RCCs must be irradiated when used in the situations listed in the paragraph concerning irradiated RCCs (see appendix B) *(Grade of recommendation: 2C+)*[38,67,109-111].

The threshold value of Hb in the neonate (10 g/dL) is higher than that in the adult and even higher (12-13 g/dL) in the first 24 hours of life or in the presence of cardiac or respiratory failure. The generally recommended doses of RCCs are 5–20 mL/kg.

For further details refer to the recommendations jointly issued by the Italian Society of Neonatology and the Italian Society of Trasfusion Medicine.

## Inappropriate indications for the use of RCCs

- Anaemia with Hb above 10 g/dL (in the absence of specific risk factors related to the patient's clinical characteristics)[3-12,14,27,67];
- to expand circulatory volume;
- to replace haematinics (iron, vitamin $B_{12}$, folates);
- for re-constituent purposes;
- to accelerate the healing of wounds.

## Monitoring indices for clinical auditing

The use of transfusion therapy with RCCs in the following situations:

- Anaemia with Hb > 10 g/dL.
- To expand circulatory volume.
- To replace haematinics.

## Indications for specifically treated RCCs

### 1. Leucodepleted RCCs

The indications for the use of leucodepleted blood components are currently under debate and need to be confirmed by the results of controlled clinical trials.

- **Consolidated indications** *(Grade of recommendation: 1C)*[67,105,106,108].

1. Prevention of febrile non-haemolytic transfusion reactions (FNHTRs) caused by the presence of antibodies to white blood cells:
   - patients with recurrent FNHTR;
   - patients who need prolonged transfusion support.
2. Reduction of the incidence of CMV infections in:
   - CMV-negative patients with congenital or

acquired immunodeficiency;
- CMV-negative recipients of a BMT from a CMV-negative donor;
- pregnant women, independently of their CMV serological status, given the possible immunomodulatory effect of the transfusion (re-activation of CMV).

3. Reduction of the risk of rejection in candidates for haematopoietic stem cell transplantation.
4. Prevention of refractoriness to platelet transfusion.
5. Intrauterine transfusions and transfusions to premature babies, neonates, and paediatric patients up to 1 year old.

- **Possible indications**

1. Candidates for renal transplantation: the use of leucodepleted red cells prevents HLA alloimmunisation and avoids the risk of transmission of CMV[106-108].
2. Immunomodulation: there is not sufficient evidence to recommend routine use of leucodepleted RBCs in surgical patients, with the aim of preventing post-operative infections or recurrent neoplasms[105,106,108,114-116].

**2. Irradiated RCCs**

Irradiation, at the dose of 25-50 Gy, is currently the only method available for preventing transfusion-related GvHD[33,34,67,103,105,109-111]. The only unfavourable effect of irradiating RBCs is hyperkalaemia, due to the accelerated release of potassium from the erythrocytes. This effect is of little relevance in adults, but can cause serious problems in the case of intrauterine transfusions or exchange transfusions.

The main indications for irradiated RCCs are listed in the appendix B *(Grade of recommendation: 2C+)*[33,34,67,103,105,109-111].

**3. Washed RCCs**

- Patients with IgA deficiency *(Grade of recommendation: 2C)*[33,34,117].
- Prevention of allergic reactions not sensitive to antihistamine drugs *(Grade of recommendation: 2C)*[33,34,117].
- Post-transfusion febrile reactions, present even when leucodepleted RBCs are used *(Grade of recommendation: 2C)*[33,34,115].

**4. Frozen RCCs**

- Patients with complex immunohaematological profiles in the absence of compatible donors *(Grade of recommendation: 2C)*[33,34,118].

## Adverse reactions

Transfusion therapy with RCCs can cause adverse reactions, which are classified on the basis of their aetiopathogenesis and the time of occurrence with respect to the transfusion[1,5,8-10,14,27].

1. Immediate immunological mechanisms:
   - acute haemolytic reactions;
   - febrile non-haemolytic reactions;
   - allergic reactions (anaphylaxis, urticaria);
   - acute non-cardiogenic pulmonary oedema (transfusion-related acute lung injury – TRALI).
2. Delayed immunological mechanisms:
   - delayed haemolytic reactions;
   - GvHD;
   - post-transfusion purpura;
   - alloimmunisation.
3. Immediate non-immunological mechanisms:
   - reaction to bacterial contamination;
   - circulatory overload;
   - non-immunological haemolysis.
4. Delayed non-immunological mechanisms
   - iron overload;
   - post-transfusion infections: possible, but very rare, viral diseases and infections by protozoa (in particular malaria).

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# Appendix A

## Working methods of the study group and grades of recommendation

The process of developing these Recommendations, in compliance with the indications contained in the methodological manual of National Programme for Guidelines[1], was based on a systematic review of the literature and updating of existing recommendations on the subject: the recommendations will be discussed in a multidisciplinary context in a subsequent stage and in the relevant institutions. Furthermore, an explicit evaluation of the quality of the proof and the strength with which the single recommendations are adopted and implemented is provided[1].

The methodology used to prepare the grades of recommendations was drawn from that used by the Consensus Conference of the American College of Chest Physicians in 2004[2].

The recommendations are classified by **grade**, expressed in Arabic numbers (1,2), according to their strength, and in **letters** (A, B, C), according to the evidence and type of study.

In detail (Table I):

- **Grade 1:** the authors are certain that the benefits are greater (or less) than the costs in terms of risk and financial expenditure. This is, therefore, a strong **recommendation.**
- **Grade 2:** the authors are less certain concerning the above points and, therefore, make a weaker recommendation.

As far as regards the classification by letters:

- **Grade A:** a recommendation derived from the evidence of numerous, consistent randomised studies.
- **Grade C+:** a recommendation derived from the analysis of observational clinical studies, but with very consistent results, or from results unequivocally extrapolated from randomised studies.
- **Grade B:** the clinical studies providing the evidence were randomised, but had

important limitations (discordant results, methodological flaws).

- **Grade C:** the recommendation derives from an analysis of observational studies, with less consistent results, or from results extrapolated with a lower degree of certainty from randomised studies; recommendations based on the clinical experience/opinion of experts are also classified as grade C.

The verb "*recommend*"is used for the higher grades (1A, 1C+, 1B, 1C), while the verb "*suggest*"is used for the lower grades (2A, 2C+, 2B and 2C).

In general, any recommendation other than Grade 1A implies that the authors recognise that there are alternative interpretations of the available evidence and that there are other clinical policies that can reasonably be considered appropriate. Furthermore, even the Grade 1A recommendations cannot be applied indiscriminately in every circumstance and in every patient.

The conventional classification of evidence is based on mathematical and statistical criteria, assigning the "strength"of evidence, in order, to: meta-analysis, randomised, controlled, experimental studies, retrospective analyses, prospective follow-ups, transverse population studies, reviews, anecdotal evidence. This is correct as far as concerns the purely clinical studies, particularly therapeutic studies focused on objective outcome evaluations.

In some fields the recommendations remain weak; in others, however, data from clinical studies that have been carried out with methodological rigour in a sufficiently large population have enabled the formulation of specific and more certain recommendations.

Furthermore, it is not always possible to use the aggregated data from meta-analyses: these variables increase the margins of individual decision for each doctor and for each patient**.**

The recommendations are accompanied by indicators intended to enable clinical auditing[1].

The present document will be revised annually, to include new information that has become available in the meantime.

Each member making up the study group has signed a statement declaring a lack of conflict of interests, conforming with that adopted by the National Programmed for Guidelines[1].

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**2)** Guyatt G, Schünemann HJ, Cook D, et al. Applying the grades of recommendation for antithrombotic and thrombolytic therapy. Chest 2004; **126**: S179-87.

**Table I-** Grades of Recommendations

| Grade of Recommendation | Clarity of Risk /Benefit | Methodological strength of supporting evidence | Implications |
|---|---|---|---|
| 1A | Clear | Randomised controlled trials without important limitations | Strong recommendation; can apply to most patients in most circumstances without reservation |
| 1C+ | Clear | No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies | Strong recommendation; can apply to most patients in most circumstances |
| 1B | Clear | Randomised controlled trials with important limitations (inconsistent results, methodological flaws) | Strong recommendations; likely to apply to most patients |
| 1C | Clear | Observational studies | Intermediate-strength recommendation; may change when stronger evidence is available |
| 2A | Unclear | Randomised controlled trials without important limitations | Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values |
| 2C+ | Unclear | No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies | Weak recommendation; best action may differ depending on circumstances or patients' or societal values |
| 2B | Unclear | Randomised controlled trials with important limitations (inconsistent results, methodological flaws) | Weak recommendation; alternative approaches likely to be better for some patients under some circumstances |
| 2C | Unclear | Evidence obtained from respected authorities or from expert committee reports or opinion of the group of experts responsible for these recommendations | Very weak recommendations; other alternatives may be equally reasonable |

# Appendix B

## Available forms of red blood cell concentrates

1. **Red blood cell concentrate**: a blood component obtained by removing part of the plasma (and a variable number of platelets) from whole blood by centrifugation, without further manipulation or addition of additive solutions. This product contains all the RBCs initially present, most of the leucocytes (2.5 –3 x $10^9$) and a variable number of platelets (related to the method of centrifugation used). The Htc is between 65 and 75%, the minimum Hb content is 45 g. The volume of a RBC concentrate is 280 ± 50 mL. The concentrated RBC, prepared without interrupting the closed circuit, must be stored at + 4 °C (± 2 °C); the storage period depends on the type of anticoagulant used (the shelf-life for units anticoagulated with CPDA-1 solution is 35 days).
2. **Red blood cell concentrate deprived of the buffy-coat**: a blood component obtained by using centrifugation to separate part of the plasma and the leucocyte-platelet layer (buffy-coat - 20 - 60 mL volume) from the RBCs. The Htc of this blood component is between 65 and 75%. The unit must contain the original amount of RBCs, except 10 - 30 mL. The white cell content must be below 1.2 x $10^9$ and the mean platelet count < 20 x $10^9$ per unit. The minimum content of Hb in each unit is 43 g; the volume is 250 ± 50 mL. The potential duration of storage is the same as that indicated for the RBC concentrates.
3. **Red blood cell concentrate with additive solution**: a blood component obtained from whole blood after centrifugation and removal of the plasma, with subsequent addition of appropriate nutrient solutions to the RBC concentrate. The volume of the additive solution is between 80 and 110 mL. The Htc depends on the quantity of the additive solution, the method of centrifugation and the amount of residual plasma, and must be between 50 and 70%. Each unit must have a minimum Hb content of 45 g. The product contains all the initial starting RBCs and, unless removed, most of the leucocytes (from 2.5 to 3 x $10^9$) as well as a variable number of platelets, depending on the method of centrifugation used. The volume differs according to the method of preparation used. The shelf-life is related to the type of additive solution used (SAG-M: 42 days).
4. **Red blood cell concentrate deprived of the buffy-coat and resuspended in additive solution**: a blood component obtained from whole blood by centrifugation and removal of both the plasma and buffy-coat, with subsequent resuspension of the RBCs in appropriate nutrient solutions. The volume of the additive solution is between 80 and 110 mL. The Htc of this blood component depends on the volume of the additive solution, on the method of centrifugation used and on the volume of residual plasma, and must be between 50 and 70%. Each unit must contain at least 43 g Hb at the end of the preparation procedures. The unit must contain all the initial RBCs, except a portion of no more than 30 mL. The leucocyte and platelet counts must be < 1.2 x $10^9$/unit and < 20 x $10^9$/unit, respectively. The volume differs in relation to the method of preparation used. The shelf-life depends on the additive solution used (SAG-M: 42 days).
5. **Washed red blood cells**: a blood component obtained from whole blood after centrifugation, removal of the plasma and subsequent washing with isotonic solutions at + 4 °C. This is a suspension of RBCs from which most of the plasma, leucocytes and platelets have been removed. The Htc can vary according to clinical needs, but should remain between 65 and 75%. At the end of the washing procedure, each unit must contain a minimum of 40 g Hb and no more than 0.3 g of protein. The product must be stored at + 4 °C (± 2 °C) for as short a period

as possible, but, in any case, no more than 24 hours, unless methods ensuring the integrity of the closed circuit are used.

6. **Leucodepleted red blood cells**: a blood component obtained by removing most of the leucocytes from a RCC by in-line pre-storage filtration or post-storage filtration in the laboratory or at the bedside. The white blood cell count must be between < 1 x $10^6$/unit, but preferably < 0.5 x $10^6$. The Htc must be between 50 and 70%. The Hb content must be at least 40 g. If the system is opened in order to prepare the product, the storage period must not exceed 24 hours at + 4 °C (± 2 °C).
7. **Frozen red blood cells**: a blood component obtained by freezing RCCs (within 7 days of collection) with an appropriate cryoprotectant and storing at a temperature between –60 °C and -80 °C in a mechanical freezer, if using a method involving a high concentration of glycerol, or at lower temperatures in liquid nitrogen, if using a method involving a low concentration of glycerol. The frozen RBCs can be preserved for up to 10 years; their use for transfusion purposes is dependent on them fulfilling the criteria for suitability laid out by existing legislation and that they have been stored at all times at the correct temperature. The indications for freezing are: storage of units of rare groups and phenotypes and, in special cases, autologous blood. Before being used, the RBCs are thawed, deglycerolised, washed, resuspended in physiological saline or additive solution and used as soon as possible; they can be stored at + 4 °C (± 2 °C) for no more than 24 hours, unless methods ensuring the integrity of the closed circuit are used. The reconstituted unit of frozen RBCs effectively does not contain proteins, leucocytes and platelets. The Htc must be between 65 and 75%. Each unit must have a Hb content of at least 36 g.
8. **Apheretic red blood cells**: a blood component obtained by collecting red blood cells using an automatic cell separator. With the cell separators currently in use, the apheresis units are usually leucodepleted. Each unit must contain a minimum of 40 g Hb and have a Htc of 65 - 70%, reduced to 50 - 70% if the RBC are resuspended in additive solution. The duration and methods of storage are the same as those for RBC concentrates.
9. **Irradiated red blood cells**: a blood component obtained by irradiating a RCC with between 25 and 50 Gy radiation. The irradiation has the purpose of decreasing lymphocyte viability and is the only method currently available for preventing transfusion-related GvHD. The product should be irradiated within 14 days of collection and irradiated units must be transfused within 28 days of collection. In cases of intrauterine or neonatal transfusion, or transfusions in patients with or at risk of hyperkalaemia, the transfusion should be given within 48 hours of irradiation or the excess potassium removed from the unit.

## Main indications for irradiation of red cell concentrates

- Intrauterine transfusion and subsequent transfusion in neonates with a birth weight of ≤ 1,500 g and/or gestational age ≤ 30 weeks.
- Congenital cellular immunodeficiency.
- Transfusion with blood components donated by first or second degree relatives (excluding stem cells and lymphocyte concentrates).
- Allogeneic transplant (until the end of GvHD prophylaxis, or a lymphocyte count > 1 x $10^9$/L is reached).
- Bone marrow donation for allogeneic transplantation (allogeneic blood components transfused to the donor before and during explantation).
- Bone marrow or peripheral blood stem cell (PBSC) autologous transplantation (in the 7 days before collection of bone marrow or PBSC and up to 3 months after transplantation or 6 months for patients undergoing total body irradiation).
- Hodgkin's lymphoma and patients treated

with purine analogues (fludarabine, cladribine and deoxycoformycin).
- The use of irradiated blood components for patients undergoing chemotherapy should be decided on an individual basis, taking into account the intensity of the immunosuppression.
- When none of the above conditions are present, it is not necessary to irradiate blood components transfused to: patients with HIV infection, aplastic anaemia, patients undergoing solid organ transplantation, chemotherapy for non-Hodgkin's lymphoma, acute leukaemias and solid tumours.



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