afssaps
Agence française de sécurité sanitaire des produits de santé

# TRANSFUSION OF HOMOLOGOUS RED BLOOD CELLS: PRODUCTS, INDICATIONS, ALTERNATIVES

## FRENCH GUIDELINES

## CONTENTS

**LIST OF ABBREVIATIONS**

AHA: Acquired Haemolytic Anaemia
AMM: Autorisation de Mise sur le Marché = Marketing Authorization
CVA: Cerebral Vascular Accident
$Ca0_2$ : Oxygen Content of Arterial Blood
$CO_2$: Carbon Dioxide
DIVC: Disseminated Intravascular Coagulation
RCC: Red Cell Concentrate
CMV: Cytomegalovirus
SD: Standard Deviation
EPO: Erythropoietin
RC: Red Cells
GVH: Graft Versus Host Disease
[Hb]: Haemoglobin concentration
Ht: Haematocrit
APO: Acute Pulmonary Oedema
$O_2$: Oxygen
FFP: Fresh Frozen Plasma
LBP: Labile Blood Products
SIA: Screening for Irregular Agglutinins
RH: Rhesus
SAGM: Saline, Adenine, Glucose, Mannitol conservation medium
$Sa0_2$: Oxygen Saturation of Arterial Blood
$S\bar{v}O_2$ : Oxygen Saturation of Mixed Venous Blood
PAT: Programmed Autologous Transfusion
$\dot{T}aO_2$ : Arterial Transport of Oxygen to the Tissues
AU: Adult Unit
CU: Child Unit
$\dot{V}O_2$ : Oxygen Consumption
TBV: Total Blood Volume

## INTRODUCTION

Like many medical acts, the transfusion of red blood cells entails risks, as does abstaining from transfusion. However, such decisions still need to be taken and it is the doctor's duty to classify the different risks according to the patients situation and the current state of medical knowledge, so that the patient can benefit from the best possible therapeutic benefit/risk ratio.

In this context, Afssaps has examined the question of the risk of transmitting non-viral agents, such as new-variant Creutzfeldt-Jakob's disease. Faced with what is currently only a potential risk, but which is not widely known, there are also two contestable transfusion attitudes : the first, "too broad" , involves waiting for the transmission risk to occur, before attempting to reduce it; the second, "too restrictive", increases other well-known risks. These different problems to be avoided indicate why, among other measures, Afssaps has decided to produce a summary of new techniques in red cell transfusion and its alternatives, such as autologous blood transfusion, erythropoietin and ferruginous treatment.

The purpose of these recommendations is to improve the quality of red cell transfusion by helping practitioners in their decision-making and contributing to standardizing practice.

## 1. THE DIFFERENT RED CELL PRODUCTS AVAILABLE AND THEIR INDICATIONS

Red cell LBPs: - obtained either from one whole blood unit, or using a cells separator,
- always contain an anticoagulant, usually CPD (citrate, phosphate, dextrose),
- are not currently subjected to viral inactivation.

In patients receiving several types of LBP, a systematic check must be made to ensure the consistency of the indications of the different transformations and qualifications for each product prescribed.

**Table I: List of transformations and qualifications applicable to red cells products.**

| TRANSFORMATIONS |
|---|
| Addition of an additional storage solution |
| Leukodepletion |
| Deplasmatization |
| Cryoconservation |
| Irradiation with ionizing radiation |
| Paediatric preparation |
| Volume reduction |
| Reconstituted whole blood |

| QUALIFICATIONS |
|---|
| Phenotyped |
| Compatibilized |
| CMV negative |

The main characteristics of the transformed red cells products are detailed in *Appendix i.*

### 1.1. TRANSFORMATIONS APPLICABLE TO RED CELLS PRODUCTS

#### ♦ Leukodepletion

Regulatory obligation in France since 1 April 1998.

Leukodepleted RCC: suspension of red cells obtained aseptically by means of a process combining at least one centrifuging stage (to eliminate most of the plasma) and a filtering stage (to perform leukodepletion). It may be produced from a unit of whole blood or from an RCC after centrifuging. The conservation solution is SAGM (saline, adenine, glucose, mannitol). The conservation solution and the leukodepletion help to reduce storage lesions on the red cells and thus extend the RCC storage period to 42 days. RCC-SAGM contains a residual quantity of plasma (up to 25 mL), platelets (non-standardized residual quantity) and leukocytes ($\leq 1.10^6$).
Leukodepletion is intended to reduce the numerous unwanted effects of transfusion, in terms of anti-HLA allo-immunization, reactions involving shivering-hyperthermia and transfusional transmission of intra-leukocyte viruses (CMV, HTLV).

Although the transfusion of LBP has an immuno-suppressant effect, leukodepletion appears not to have any effect for the prevention of tumour relapse and its effect in terms of post-operative infections remains controversial.

Indication for leukodepleted RCCs
Used when there is no indication of specific transformation or qualification.
NB: Non-leukodepleted RCCs are authorized for certain transfusion protocols prior to organ transplants (decree dated 30 March 1998).

In neonates**,** the quantity of SAGM injected is usually less than the toxicity threshold of its various components; it can therefore be used extensively, as in adults.
Leukodepleted RCC-SAGM is not used in cases of massive transfusion (≥ 1 blood volume) (Professional Agreement). In such situations, either leukodepleted or reconstituted whole blood can be used.

- **Deplasmatization**

Leukodepleted, deplasmatized RCCs contain less than 0.5 g of extracellular proteins, have a very low platelet content and must be used within 6 hours.

Indications for deplasmatized, leukodepleted RCCs (Professional Agreement)
- Patients with plasma protein intolerance: history of major anaphylactic transfusion reactions (extensive urticaria, bronchospasm and Quincke's oedema, anaphylactic shock, anti-IgA antibodies).
- History of post-transfusion purpura (deplasmatization ensures platelet removal).

Their use remains in debate in the event of a history of repeated minor anaphylactic transfusion reactions (urticaria, cutaneous rash). It is no longer justified in patients suffering from paroxysmal nocturnal haemoglobinuria.

In neonates, deplasmatization is necessary when the product to be transfused contains a potentially dangerous antibody and if there is no alternative.
This means that "paediatric preparations" are impossible for technical reasons; its advantages must be weighed against the advantages of these preparations (use of a single donor).
Because of the presence of maternal IgG antibodies in the blood of the foetus and up to 3 months after birth, the red cells must be compatible with the child's and the mother's ABO group. This situation may lead, particularly in cases of massive transfusion, to the use of deplasmatization to reduce the concentration of anti-A and/or anti-B antibodies in the RCC.

- **Cryoconservation**

This enables long-term storage of viable, functional red cells.

Depending on the storage temperature (-30°C, -80°C or -130°C), the storage duration ranges from 4 months to more than 20 years.

It is possible to keep them for 7 days after thawing, subject to two conditions:
- the freezing and thawing processes must have been performed in a functionally-closed circuit;
- a specific conservation solution must be used.

The RCCs have a plasma protein concentration similar to that of deplasmatized RCCs (< 0.5 g per product) and a low residual level of platelets and leukocytes (< $10^6$)

Indications for cryoconserved leukodepleted RCCs
- Patients with a rare or exceptional red cells phenotype ("negative public");
- Patients with multiple anti-red cells antibodies.

An individual reserve is built up when transfusion is planned (scheduled operation, beginning of pregnancy, etc.).
Cryoconserved leukodepleted RCCs can be used for the same indications as deplasmatized leukodepleted RCCs, but their use is not operational on a large scale.
There are no specific indications in neonates.

### ♦ Irradiation with ionizing radiation

This involves exposing leukodepleted RCCs to a 25 to 45 Gy dose of ionizing radiation (French regulations) to prevent post-transfusional GVH disease.

Indications for irradiated leukodepleted RCCs (Grade C)
- Patients with cellular congenital immunodeficiency;
- Before or during sampling of autologous, medullar or blood haematopoietic stem cells;
- Patients treated by grafting of autologous or allogenic haematopoietic stem cells, as soon as conditioning begins, for 1 year after an autologous graft and for life after an allogenic graft;
- Patients treated with fludarabine;
- Transfusion of RCCs resulting from organized donation inside the family, whatever the degree of relationship between donor and receiver (regulatory obligation).

However, the following indications are not the subject of a professional agreement:
- Hodgkin's disease undergoing treatment;
- Chemotherapies for non-Hodgkins lymphoma, acute leukaemia or solid tumours;
- People who have received organ transplants.

In these last two situations, it only appears justified in cases of profound immunosuppression.

For the foetus and neonates, irradiation is recommended in the event of intra-uterine transfusion, exsanguino-transfusion or massive transfusion (> 1 blood volume) in premature babies.
In paediatric onco-haematology, RCCs are usually irradiated systematically (Professional Agreement).

### ♦ Paediatric preparation

This involves aseptic division of a leukodepleted RCC into several units. A single donation leads to production of several units that can be used successively for the same patient.

Indication for paediatric preparations
- Repeated red-cell transfusions in neonates, in order to reduce the number of donors.

### ♦ Volume reduction

This involves aseptic elimination of part of a leukodepleted RCC's suspension medium by centrifuging. The haematocrit (Ht) is then between 70 and 85%.

Indication for volume reduction
Essentially neonates, in two circumstances :
- when strict control of the volume injected is necessary,
- massive transfusion, when it is required to eliminate the majority of the conservation solution in the liquid phase.

### ♦ Reconstituted whole blood

This is an aseptic mixture of a leukodepleted RCC with either 4% albumin or FFP. Reconstitution is usually performed with FFP to prevent the coagulation problems that could arise if albumin is used. There are no studies demonstrating the benefits and disadvantages of these 2 products. It must be carried out by the blood transfusion centre.

Indication for reconstituted whole blood*:*
- Essentially in neonates, for exsanguino-transfusions or cardio-respiratory assistance techniques.

Reminder of the only indication for "whole blood": massive transfusion in neonates, as long as the child's and the mother's ABO groups allow the use of red cells and plasma from the same group.

### 1.2. QUALIFICATIONS APPLICABLE TO RED CELLS PRODUCTS

#### ♦ Phenotyping[1]

This applies to all the RCCs antigen-compatible with the recipient for the 5 following antigens: RH2 (C), RH3 (E), RH4 (c), RH5 (e) in the RH (Rh) systems and KEL1 (K) in the KELL (Kell) system.
It is described as "extended" when, as well as the RH-KELL phenotype, at least one antigen from other system (Duffy, Kidd, MNS, Lewis, etc.) is antigen-compatible with the recipient.

Indications for RH and KELL phenotyped leukodepleted RCCs
The RH and KELL phenotyped RCCs are:
- strictly prohibited in:
  - patients who have or have had one or more red cells allo-antibodies, apart from those considered of no interest in the context of transfusion, in order to prevent transfusion-related haemolytic accidents (regulatory obligation),
  -women, from birth until the end of the procreative period, in order to prevent the appearance of anti-red cells allo-antibodies which increase the risk of foetal-maternal haemolytic accidents (regulatory obligation),
  - neonates in the presence of an anti-red cells antibody (from the mother), whatever the sex;
- recommended in patients receiving iterative RCC transfusions to prevent the appearance of anti-red cells allo-antibodies (Grade C) ;
- advisable for any patient of either sex with a reasonable life expectancy (Professional Agreement).

Non-indication for RH and KELL phenotyped RCCs
- Patients who test negative for SIA and who have reduced life expectancy.

The respect of the phenotype extended to one or more blood-group antigens other than ABO, RH and KELL depends on the antibodies detected in immunized patients. In these patients, it is advisable to respect the RH and KELL phenotypes for preventive purposes.
The phenotype extended to the antigens FY1 ($Fy^a$), JK1 ($Jk^a$) and MNS3 (S) may if necessary be proposed as a preventive measure in patients dependent on RCC transfusions over the long term, particularly in patients with sickle cell disease or thalassanaemia.

#### ♦ Compatibility

The direct test for RH-KELL phenotyped RCCs is a non-systematic analysis that complements the test for irregular anti-red cells antibodies. It involves testing the recipient's serum in terms of the red cells contained in the tubing of the RCC to be transfused, and then assigning this RCC the qualification "compatibilized" if the test proves negative. The maximum period of validity for this test is 3 days from the date when the sample was taken from the recipient. The compatibilized RCC bears the following information: identity of the recipient, test date and period of validity (regulatory obligation).

Indications for compatibilized leukodepleted RCCs
- Any patient showing or having shown or suspected of showing signs of one or more anti-red cells allo-antigens regarding RH-KELL phenotyped RCCs, unless it is a life-threatening emergency (regulatory obligation).
- In neonates, if anti-red cells antibodies are present, the RCCs are compatibilized in terms of serum from the mother, the source of the antibodies. If this serum is unavailable, the child's serum is used.

#### ♦ CMV negative

This qualification applies to RCCs from donors in which the test for anti-CMV antibodies is negative at the time of blood donation.
Its availability is limited because of the high seroprevalence (50 to 80%) of anti-CMV antibodies among blood donors.
It should be noted that, as CMV's location is nearly exclusively intra-leukocyte (monocytes), leukodepletion alone helps to prevent its transmission, without allowing it to be determined whether association of the two methods provides better prevention.

[1] The new naming conventions for blood group antigens is used in this paper; the former names are included in brackets for didactic reasons. The correspondence between the two naming systems is shown in *Appendix II*.

Indications

Because of the small amounts of CMV-negative RCC available and the doubts concerning its superiority to leukodepleted RCC, the indications need to be listed in order of importance.

The following indication should be given priority (Professional Agreement):

- allografts of haematopoietic stem cells in situations where both the donor and recipient are CMV-negative.

Within the limits of product availability (Grade C):

- CMV-negative pregnant women;
- premature babies born after less than 32 weeks of gestation, when the mother is seronegative for CMV ;
- recipients of lung transplants, whatever their serological status regarding CMV.

However, the following indications are not the subject of a professional agreement:

- CMV-negative patients awaiting grafts, in order to preserve their chances of remaining CMV-negative;
- CMV-negative recipients of grafts other than haematopoietic stem-cell or lung grafts, when the donor is CMV-positive;
- CMV-positive recipients of grafts.

**Table II: Main indications of the products transformed and qualified.**

| Transformation | Indications |
|---|---|
| LEUKODEPLETION | All LBPs since 1st April 1998 |
| Deplasmatization | Plasma-protein intolerance<br>History of post-transfusional purpura |
| Cryoconservation | Same indications as for deplasmatization.<br>+<br>Rare red cells phenotype<br>Poly-immunized patient |
| Irradiation | Congenital cellular immune deficiency<br>Before and during sampling of autologous haematopoietic stem cells<br>Patients treated by grafting of autologous and allogenic haematopoietic stem cells, for 1 year after an autologous graft and for life after an allogenic graft<br>Certain intensive anti-cancer polychemotherapies<br>Intra-uterine transfusion<br>Exsanguino-transfusion and massive transfusion in premature babies<br>Directed intra-family donations (governed by regulations) |
| **Qualification** | **Indications** |
| Phenotyped | Patients with one or more red cells allo-antibody (regulatory)<br>Patients of reproductive age (regulatory)<br>Patients receiving iterative transfusions<br>Advisable for any patient with a reasonable life expectancy |
| Compatibilized | Patients who present or have presented or have been suspected of presenting one or more red cells allo-antibodies (regulatory) |
| CMV negative | Allografts of haematopoietic stem cells in situations where both the donor and recipient are CMV-negative. |

## 2. TRANSFUSION OF RED CELLS IN EMERGENCY CASES INVOLVING HAEMORRHAGE, ANAESTHESIA OR , RESUSCITATION

### 2.1. ACUTE ANAEMIA: GENERAL COMMENTS

This mainly covers anaemia due to haemorrhages.

The necessity of transfusing red cells arises from the need to increase arterial transport of $O_2$ to the tissues.

Physiological reminder

$\dot{T}aO_2 = \dot{Q} \times CaO_2 \approx \dot{Q} \times SaO_2 \times [Hb] \times 1,39$

The critical threshold ($\dot{T}aO_2$ crit) in man under anaesthetic is approximately 5 $mLO_2.kg^{-1}.min^{-1}$ (Grade B). To maintain a sufficient safety margin, the safety threshold in adults is set at 10 $mLO_2.kg^{-1}.min^{-1}$ (Professional Agreement).

This physiological data shows that tolerance of acute anaemia depends on the possibilities of increasing cardiac output, which explains why emergency correction of the hypovolaemia is necessary and also why the transfusion threshold is higher among people suffering from heart failure. An increase in $\dot{V}O_2$ (fever, agitation, etc.) reduces tolerance of anaemia.

Transfusion threshold

The concept of a transfusion threshold is criticized because transfusion is a complex decision based on data such as the haemoglobin concentration ([Hb]), cardiac reserve, estimation of the bleeding rate and clinical tolerance. However, the idea that there are practically no situations requiring a concentration higher than 10 $g.dL^{-1}$ is not called into question. A threshold of around 7 $g.dL^{-1}$ is usually accepted during anaesthesia of patients without a history of cardio-vascular disease.

For patients with a history of cardio-vascular problems, there is no demonstrated benefit from concentrations higher than 8 $g.dL^{-1}$. It seems reasonable to maintain the threshold of 10 $g.dL^{-1}$ in cases of proven, life-threatening cardiac pathology.

To sum up, with all the reservations pertaining to the concept of a threshold, the following thresholds have been defined (Professional Agreement) :

- 7 $g.dL^{-1}$ in people with no particular history;
- 8-9 $g.dL^{-1}$ in people with a history of cardio-vascular disease;
- 10 $g.dL^{-1}$ in people clinically intolerant of lower concentrations or suffering from acute heart failure or proven heart failure.

These values are not applicable below the age of 2 years because of the increase in the $\dot{T}aO_2$ value: modification of the affinity of Hb for $O_2$, increased $O_2$ consumption by the body, reduction in adaptation capabilities by reducing the heart's inotropic reserves. Furthermore, the presence of respiratory distress may lead to hypoxaemia.

Indications in cases of acute anaemia (Professional Agreement)

- State of shock despite correction of the hypovolaemia,
- Despite correction of the hypovolaemia, persistence of the symptoms of poor tolerance associated with a fall in [Hb].

**Table III: Symptomatology according to the amount of blood lost in adults without comorbidity**

| Blood loss (ml) | **750** | **800-1,500** | **1,500-2,000** | **> 2,000** |
|---|---|---|---|---|
| Systolic AP | Unchanged | Normal | Reduced | Very low |
| Diastolic AP | Unchanged | Increased | Reduced | Very low or unmeasurable |
| Pulse ($min^{-1}$) | Moderate tachycardia | 100-120 | > 120 (low) | > 120 ( very low) |
| Capillary refilling | Normal | Slow (> 2 s) | Slow (> 2 s) | Undetectable |
| Respiratory frequency | Normal | Normal | Tachypnoea (> 20 $min^{-1}$) | Tachypnoea (> 20 $min^{-1}$) |
| Urinary output ($mL.h^{-1}$) | > 30 | 20-30 | 10-20 | 0-10 |
| Extremities | Normal | Pale | Pale | Pale and cold |
| Colouring | Normal | Pale | Pale | Grey |
| Mood /consciousness | Normal | Anxiety or aggression | Anxiety or aggression or altered | Altered or coma |

**Table IV: Classification of the symptoms according to the amount of blood lost in children.**

- *Blood loss less than 15% of total blood volume (Class 1)*
  - normal arterial pressure
  - cardiac frequency increased by 10 to 20%
  - no modification of cutaneous capillary refill time
- *Blood loss between 20% and 25% of total blood volume (Class 2)*
  - tachycardia > 150 $min^{-1}$
  - tachypnoea > 35-40 $min^{-1}$
  - increase in cutaneous capillary refill time
  - reduction in arterial pressure
  - reduction in amplitude of pulse
  - orthostatic hypotension > 10-15 mmHg
  - urinary output > 1 $mL.kg^{-1}.h^{-1}$
- *Blood loss between 30% and 35% of total blood volume (Class 3)*
  - all the above signs are present
  - urinary output < 1 $mL.kg^{-1}.h^{-1}$
  - sleepiness, vomiting, sweating, agitation
- *Blood loss greater than 50% of total blood volume (Class 4)*
  - undetectable pulse
  - confusion

The most frequent signs of severe acute anaemia are: syncope, dyspnoea, tachycardia, angina, orthostatic hypotension, transient ischemic attack.
The search for clinical arguments must integrate the patient's ability to adapt to the fall in $O_2$ transport. This ability is high in young, healthy patients, but limited in older subjects and patients with heart or respiratory disease. A known or symptomatic heart condition is the main factor limiting the increase in cardiac output and this increases morbidity and mortality.

*In young, healthy subjects*, excessive polypnoea, tachycardia higher than 130 $min^{-1}$ or persistent hypotension should lead to the examination of RCC transfusion as a solution.

*In an older subject or a patient with aortal narrowing*, the appearance or aggravation of angina or modifications (including asymptomatic changes) of the ECG indicating myocardial ischemia are an indication, as is the appearance of a neurological deficit (including transient) in old patients or subjects suffering from a vascular pathology.

*In a subject with heart or respiratory disease*, altered vigilance, effort-related faintness or persistent hypotension are in favour of transfusion, as does a significant fall in $APO_2$.

β-blockers and bradycardial calcium inhibitors, which limit the efficacy of the compensating mechanisms, must be taken into account for the transfusion decision.
Whether or not the patient is transfused, symptoms of poor tolerance which are persistent or indicate a renewal of bleeding must be searched for regularly.
Any transfusion decision and monitoring information must be recorded and explained in the patient's file.

Volume to be transfused
The transfusion is performed preferably on a peripheral vein.
The number of RCCs to be transfused ($N_{CGR}$) depends on:
- the quantity of Hb present in each RCC ($QHb_{CG}$) ;
- the total blood volume of the patient (TBV in mL) ;
- the initial Hb concentration ($Hb_i$ in $g.dL^{-1}$) ;
- the final expected Hb concentration ($Hb_d$ in $g.dL^{-1}$).

$$N_{CGR} = (TBV / 100) (Hb_d - Hb_i) / QHb_{CG}$$

The TBV can be calculated either using charts taking into account the weight and size, or by using Gilcher's rule of 5.

**Table V: Gilcher's rule of 5 for calculating the TBV.**

| | | |
|---|---|---|
| Woman | obese: 60 mL.kg$^{-1}$<br>slim: 65 mL.kg$^{-1}$ | normal: 70 mL.kg$^{-1}$<br>athletic: 75 mL.kg$^{-1}$ |
| Man | TBV for woman + 5 mL.kg$^{-1}$ | |
| Child over 1 year old | identical to adult woman (70 mL.kg$^{-1}$) | |
| Infant under 1 year old | 70-75 mL.kg$^{-1}$ | |
| Neonate | 75-85 mL.kg$^{-1}$ | |

*In children*, the volume is calculated while taking into account the fact that 3-4 mL.kg$^{-1}$ of RCC raises [Hb] by 1 g.dL$^{-1}$.

*In pregnant women or patients aged more than 70 years,* no formula can be used to evaluate the quantity of RCC to transfuse, which is the minimum quantity causing disappearance of the signs of poor tolerance and/or the achievement of an acceptable Hb concentration.

*In adults*, transfusion is performed on the basis of an RCC capable of causing the symptoms of poor tolerance to disappear. The attitude which stipulates that it is not a good idea to transfuse a single RCC is obsolete. According to the formula indicated, an RCC is expected to increase [Hb] by 1.4 g.dL$^{-1}$ in a 50 kg woman and by 0.7 g.dL$^{-1}$ in a 90 kg man.

Correction speed

No studies have determine the optimum correction speed, particularly in patients with heart failure.

Perfusion rates customarily used:
- in adults: 10 to 15 mL.min$^{-1}$, i.e. 1 RCC in 20 minutes;
- in neonates: 3 to 15 mL.kg$^{-1}$.h$^{-1}$.

The maximum rate is limited by:

- the potentially harmful effects of a massive intake of red cells:
  - haemodynamic complications, dominated by acute pulmonary oedema;
  - hyperkaliaemia resulting from rapid intake of potassium (in practice, only has consequences in paediatrics or in subjects with renal failure, as the effect is usually minimal in normal adults) ;
  - hypothermia (reheating of the RCCs with thermostatically-controlled equipment is necessary);
- the means of perfusion used. Acceleration of transfusion can be achieved, in ascending order of efficacy: by gravity (raising the flask), by using a *blood pump*, a manually-inflated pressure sleeve or a lobe pump with an air bubble detection system with a non-neutralizable alarm.

### 2.2. ACUTE ANAEMIA DURING A SURGICAL OPERATION

There is no consensus concerning the acceptable level of haemodilution. Relatively low Hb concentrations are often well tolerated under anaesthesia. The amount of bleeding observed may justify transfusion immediately.

#### ♦ In pre-operative conditions

If there are pre-operative signs of poor tolerance, whether the anaemia is acute or chronic, the situation is exactly the same as indicated above. There is no data enabling pre-operative transfusion to be given priority in principle. The supposed condition of the coronary arteries and the left ventricular function are the main factors for the decision.

In the absence of pre-operative signs of poor tolerance, there is no data justifying modification of the transfusion threshold in cases of non-haemorrhagic minor operations, simply because there is an operation or anaesthesia.

#### ♦ During operations

Transfusion is frequently necessary when pre-operative [Hb] is < 8 g.dL$^{-1}$ and bleeding during the operation is greater than 500 mL.

An [Hb] of around 7 g.dL$^{-1}$ is usually well tolerated in young subjects without medical pathology or well-compensate chronic anaemia. It is advisable to regularly monitor the haematocrit or, even better, haemoglobin during haemorrhagic

surgery. In subjects with a heart pathology or if [Hb] < 7 g.dL$^{-1}$, monitoring of $S\bar{v}O_2$ can be recommended. In patients with heart failure, screening for myocardial ischemia by monitoring the ST segment is recommended.

♦ **In post-operative conditions**

The metabolic constraint is higher, while monitoring usually becomes less intensive than in the operating theatre, as time passes.
Recommended transfusion threshold: [Hb] = 8 g.dL$^{-1}$. There are no studies showing a reduction in morbidity or mortality for [Hb] > 8 g.dL$^{-1}$, including among patients in intensive care (Grade B).
In fact, the final decision is a clinical one. Basically, there are two possible attitudes:

- either adapt the treatments and monitoring to the level of haemodilution,
- or adapt the level of haemodilution to the therapeutic and monitoring possibilities.

The absence of chilling achieved by maintaining normal temperature or continuation of anaesthesia and monitoring in intensive care may allow haemodilution rates comparable to those during operations, when there are no complications. However, signs of chilling, fever or agitation or ordinary monitoring on the ward may cause a higher Hb concentration to be preferred (Professional Agreement).

In the event of myocardial infarction in the acute stage, unstable angina and left ventricular failure, it seems reasonable to remain above the threshold of 10 g.dL$^{-1}$. In subjects with heart failure not accompanied by any acute pathology, there are no arguments for recommending an [Hb] threshold > 8 g.dL$^{-1}$. Transfusion is adapted to the observed rate of bleeding, in order to maintain [Hb] > threshold (Professional Agreement). Screening for myocardial ischemia by monitoring the ST segment is recommended.

These recommendations also apply to pregnant women and children over 2 years of age.

*The methods for saving homologous blood are dealt with in Chapter 6.*

### 2.3. PRODUCTS TRANSFUSED IN EMERGENCY CASES

The conflict between the importance of transfusing without losing precious time and the importance of using products corresponding to the qualifications considered useful means that the degree of urgency must be specified, distribution must be organized to facilitate access to the most suitable and a decision-making algorithm must be formalized.
RCC distribution will be carried out with products whose qualification is as close as possible to the patient's red cells phenotype. It will take into account:

- women of reproductive age,
- patients with anti-red cells allo-antibodies,
- subjects liable to be retransfused, with a reasonable life expectancy (see Chapter 1.2).

The qualifications which are not immuno-haematological and the transformations will not be taken into account if there are products available which exactly correspond to the patient's needs.

♦ **Immediate life-threatening emergency**

LBPs must be obtained as quickly as possible and distributed without delay. RCCs may be distributed (even if valid results are not available) without blood grouping and without screening for irregular agglutinins (SIA): O RH : -1, KEL :-1, or O RH : 1 (if possible RH :-3,-4) KEL :-1 (formerly O Rh D neg, KELL neg or O Rh D pos (if possible RH E-, c-) KELL neg) and free of haemolysin. In the presence of valid immuno-haematological data and in emergency situations, it is recommended to distribute RCCs from group KEL : -1 (KELL neg) in all cases, RH : -1 (Rh D neg) if the patient's phenotype is RH : -1 (Rh D neg), RH : 1 (Rh D pos) (RH :-3,-4 (formerly E-, c-)) if the patient's phenotype is RH : 1 (Rh D pos). The LBP prescription will specify that it is an immediate life-threatening emergency and will be accompanied by specimens for immuno-haematological analysis as soon as possible.

- **Life-threatening emergency**

LBPs should be obtained within 30 minutes. The RCCs must be distributed with the right group, possibly without SIA if the examination is not available. The LBP prescription will specify that it is an life-threatening emergency and will be accompanied by specimens for immuno-haematological analysis. SIA will be performed as soon as possible.

- **"Relative" emergency**

The time available is usually 2 to 3 hours, which means that all the immuno-haematological examinations can be carried out (including SIA if it dates from more than 3 days previously); the LBPs distributed will be isogrouped and, if necessary, compatibilized. As the haemorrhagic situation may change at any time, it will be possible to redefine the degree of urgency.

In emergencies, there is currently no alternative to RCC transfusion.

## 3. TRANSFUSION OF RED CELLS IN CASES OF CHRONIC ANAEMIA

### 3.1. GENERAL COMMENTS

The duration of development of anaemia allowing it to be defined as "chronic" has not been established.

Indications in cases of chronic anaemia

- Correction of the symptoms associated with a reduction in [Hb].

The symptoms of chronic anaemia are: asthenia, irritability, palpitations, effort related dyspnoea, headaches and dizziness.

The non-specific, subjective nature probably explains the absence of any correlation with [Hb]. Clinical tolerance varies significantly from one individual to another, according to their physical activity.

Transfusion is only indicated when there is no etiological treatment available (treatment for iron deficiency, folates, vitamin $B_{12}$, stopping of a haematotoxic drug when possible, treatment of inflammatory disease), or when the severity of the anaemia does not allow any wait for the response to this etiological treatment.

During chronic anaemia, the indication of an RCC transfusion must be discussed according to:

- its severity, assessed on the basis of the haemoglobinaemia and clinical tolerance, taking into account the patient's compensating mechanisms (adaptability of cardiac output in particular);
- its cause and the way it has become established;
- the benefit/risk ratio of transfusion for the patient.

*The methods for saving homologous blood are dealt with in Chapter 6.*

Transfusion threshold

- [Hb] = 10 $g.dL^{-1}$ : the indications are rare and restricted to patients suffering from cardio-pulmonary disease who show signs of intolerance.
- [Hb] = 8 $g.dL^{-1}$ : the indications are restricted to patients who need to be active and are limited in their activity, as well as people with a history of cardio-vascular problems.
- [Hb] = 6 $g.dL^{-1}$ : transfusion is generally indicated, except in cases of good tolerance (Biermer's anaemia, hypoferric anaemia, certain chronic haemolytic types of anaemia, anaemia associated with chronic renal failure).

The indications for transfusions according to the age and situation are not clearly defined. In older patients, [Hb] must be interpreted according to hydration condition and possible functional renal failure. In the event of hydration problems, they must be corrected beforehand to allow more accurate assessment of [Hb].

Volume to be transfused

The only calculation method is the one defined for acute anaemia. In older people or people suffering from heart failure, transfusion is performed on the basis of one RCC at a time (Professional Agreement).

Correction speed

It must be slow for the first 15 minutes ($\leq$ 5 mL.min$^{-1}$), and can then be increased (up to 10 mL.min$^{-1}$) if there are no clinical signs of intolerance. In the event of volaemic overload, particularly in patients with heart failure, it must remain slow throughout the transfusion ($\leq$ 5 mL.min$^{-1}$); a half-sitting position and the use of diuretics may then be indicated.

### 3.2. SPECIFIC CASES

#### ♦ Older people

The clinical signs may be atypical: faintness, falls, confusion, etc. In older people, the cardiac and peripheral vasomotor compensating mechanisms are frequently altered.
If life expectancy is very short, the long-term risks of the transfusion must be weighed against the short-term benefit.
Taking the cardiovascular risk into account, it is customary not to set the transfusion threshold below 8 g.dL$^{-1}$.
The quantity of RCC to be transfused and the transfusion rate must take into account the risk of volaemic overload and its consequences (APO), particularly when there is pre-existing heart failure.

#### ♦ Pregnancy

Because of the increase in plasma volume, [Hb] falls at the end of pregnancy by 5 to 10%.
The risk of effects on the foetus should be considered when Hb < 9 g.dL$^{-1}$. Any anaemia must be investigated. Usually, the problem stems from an iron or folate deficiency, which is easy to correct and can be prevented during the last three months of pregnancy.

#### ♦ Cardiac pathology

Any fall in [Hb] may cause or aggravate myocardial ischemia. Most coronary manifestations appear to occur in patients suffering from a stenotic coronary pathology. Chronic anaemia is usually well tolerated by people with heart failure.

#### ♦ Other pathologies

No serious work has been carried out among anaemic patients, particularly older ones, with a chronic respiratory disease, an arterial disease, particularly peripheral, or a vascular or degenerative cerebral pathology, allowing to define the optimal indications of RCC transfusions.

## 4. TRANSFUSION OF RED CELLS IN HAEMATOLOGY AND ONCOLOGY

### 4.1. TRANSFUSION OF RED CELLS DURING MALIGNANT HAEMOPATHIES AND IN ONCOLOGY

#### ♦ During acute malignant haemopathies in adults and haematopoietic stem-cell grafts

Indication during acute malignant haemopathies
It must take into account the kinetics of the aplasia caused by the chemotherapy and the expected date when aplasia will end. Maintenance of [Hb] above the threshold set is even more important if the forecast date for the end of aplasia is a long time in the future.

No studies are available concerning the indications for RCCs in patients at the end of their lives. It is important to study, on a case-by-case basis, both the objective and subjective effects of anaemia, as well as the well-being genuinely provided by the transfusion, in order to avoid systematic prescription based on [Hb] alone. This benefit must be re-assessed after each transfusion and compared with the possible side effects and the simple constraints (extent of transfusion reactions in poly-immunized patients, travel necessary to perform it, etc.).

Transfusion threshold
Recommended threshold: [Hb] = 8 g.dL$^{-1}$, when spontaneous correction of the anaemia is not foreseeable in the short term (Professional Agreement).

It may be high, however, at around 9-10 $g.dL^{-1}$, in circumstances which increase $O_2$ consumption: severe infections, bronchospasm, pulmonary or cardiac complications reducing the functional cardiac reserve (myocardial ischemia, atrial fibrillation).

Products transfused
- leukodepleted RCCs, phenotyped at least in the RH and KELL phenotype, and irradiated (in the indications figuring in *Table II*).

In the specific case of allografts, the transfusion rules take into account the red cells groups of the donor and recipient, as well as the time between the graft and administration of the concentrates. For allografts of haematopoietic stem-cells in situations not involving genetic relatives, CMV-negative products remain recommended.

♦ **During chronic malignant haemopathies and in oncology in adults**

Indications during chronic malignant haemopathies and in oncology
- Indications and transfusion conditions identical to those for acute malignant haemopathies in patients receiving intensive chemotherapy with grafting of haematopoietic stem cells.
- In all other situations, chronic anaemia is a habitual, multi-factorial complication, particularly in the later stages of intensive chemotherapy or after such treatment. It may be temporary and not require systematic transfusion, particularly in young patients. It may persist and become more serious because of the development of the disease and the toxicity of the treatments used. It may then be necessary to correct it in the long term, particularly since it has been suggested that anaemia may have a negative impact on the efficacy of radiotherapy, notably in ORL and uterine cancers.

Transfusion threshold
Recommended threshold: the level at which the symptoms of anaemia disappear, without usually going below the threshold of 8 $g.dL^{-1}$ (Professional Agreement).
Transfusing above this threshold exposes the patient to the complications of hypertransfusion when the prognosis indicates a life expectancy of several years.
This threshold may be higher (10 $g.dL^{-1}$) if the anaemia is not well tolerated, particularly in the event of dyspnoea during bronchial cancer or symptomatic lung metastases, notably in older patients (Professional Agreement).

*The methods for saving homologous blood are dealt with in Chapter 6.*

♦ **In paediatric oncology**

Indication in paediatric oncology
- Symptomatic anaemia (Professional Agreement). Tolerance of anaemia in children is good and it does not usually require urgent correction.

Transfusion threshold
Recommended threshold: [Hb] = 8 $g.dL^{-1}$ (threshold for which there are physiopathological arguments in adults) in children receiving continuous chemotherapy giving no hope of spontaneous correction of their anaemia in the short or medium term.

*The methods for saving homologous blood are dealt with in Chapter 6.*

Products transfused
- phenotyped leukodepleted RCCs. Phenotyping is justified in female children and by extension all children because of their age and the risk of allo-immunization which may have a long-term impact (probable polytransfusions). The indications for irradiation are the same as in adults, but tend to be extended to avoid as far as possible the onset of post-transfusional GVH (Professional Agreement).

Volume to be transfused
It must be sufficient to raise [Hb] to a level liable to delay a repeat transfusion, with the aim of reducing the number of donors. The other approach designed to reduce transfusion risk involves the use of paediatric preparations for low-weight children.

The formula defined concerns acute anaemia can be used, but the following formula is widely used in paediatric oncohaematology to estimate the volume to be transfused:

$$\text{Volume to transfuse (in mL of RCC)} = W \times \Delta Hb \times (3 \text{ to } 4)$$

(W: weight in kg ; $\Delta$Hb : required level of [Hb] in $g.dL^{-1}$).

### 4.2. TRANSFUSION OF RED CELLS DURING HAEMOGLOBULINOPATHIES

#### ♦ Homozygous major β-thalassaemia ("Cooley's anaemia")

As these patients have very low spontaneous Hb production, transfusions condition the vital prognosis.

Transfusion threshold

Recommended threshold in children and adolescents: [Hb] = 10 $g.dL^{-1}$, a threshold which allows normal educational, leisure or professional activities, while reducing the developmental problems and the erythroid hyperplasia responsible for morphological deformations. The immunological, infectious and iron-overdose risks linked to transfusion are the reasons why a higher threshold has not been chosen. The transfusions consist of 15 $mL.kg^{-1}$ every 3 weeks or 20 $mL.kg^{-1}$ every 4 weeks.

The transfusion threshold may be lower in adults: 8 to 9 $g.dL^{-1}$.

Annual consumption

Annual consumption of approximately 150-200 mL/kg/year of SAGM-RCC usually maintains a mean [Hb] close to 12 $g.dL^{-1}$. Consumption greater than 200 mL/kg/year should lead to investigation of the inefficacy of transfusion, often due to hypersplenism, raising the question of splenectomy.

Products transfused

- RH-KELL phenotyped leukodepleted RCCs: before the first transfusion, it is recommended to carry out extended phenotyping (RH, KELL, Kidd, Duffy, MNS, etc.). The use of young red cells (neocytes) doubles the number of donors and is not therefore recommended, although it allows greater spacing of transfusions.

#### ♦ Homozygous thalassaemia intermedia

These patients have a spontaneous Hb production of 7 to 10 $g.dL^{-1}$.

Indications during homozygous thalassaemia intermedia

- Aggravation of chronic anaemia: this may be acute (infection, erythroblastopaenia) and then requires transfusion. It may be progressive and indicate hypersplenism; splenectomy then reduces or removes the need for transfusions.
- Signs of intolerance of chronic anaemia: fatigability, educational or professional impact, delayed puberty, etc.

Transfusions may be necessary during pregnancy.

#### ♦ Homozygous drepanocytosis

We group homozygous drepanocytosis sufferers with patients with sickle-cell anaemia syndromes which are similarly severe (patients with heterozygous S β-thalassaemia) or less severe (heterozygous SC patients).

In all patients, an [Hb] of 8 ± 1 $g.dL^{-1}$ allows normal activity and growth. It is not necessary to transfuse a healthy sickle-cell patient with [Hb] $\geq$ 6 $g.dL^{-1}$.

Indications for simple blood transfusion

The purpose of the transfusion is to return the haemoglobinaemia to its base value. A reduction in Hb compared with the basic concentration may be due to several mechanisms:

- Hyperhaemolysis caused by an infection or contemporary with a vaso-occlusive episode: the transfusion indication is discussed according to clinical tolerance and the extent of the reticulocyte response.
- Infection with parvovirus B19: reticulocytopaenia leads to the diagnosis. Transfusion is usually necessary
- A transient reduction in erythropoiesis contemporary with an acute inflammatory syndrome: the transfusion indication is discussed according to clinical tolerance and the speed of the rise in the reticulocyte concentration.

- Sequestration of the spleen: this may be acute: the diagnosis is based on rapidly developing splenomegaly accompanied by sudden loss of circulating red blood cells. This is a transfusion emergency. The sequestration may become chronic, leading to a need for repeated transfusions. In such cases, splenectomy should be considered.

Products transfused
- phenotyped leukodepleted RCCs. Before the first transfusion, it is recommended to carry out extended phenotyping (RH, KELL, Kidd, Duffy, MNS, etc.). The RH and KELL systems are usually sufficient, as the risk of allo-immunization in the other systems appears low in sickle-cell patients. The appearance of an allo-antibody must lead to extension of the phenotype compatibility of the RCCs transfused.

Indications for occasional exchange transfusion
This is a transfusion operation combining bleeding and transfusion, with the aim of reducing the HbS concentration while leaving the Ht at approximately the same level. It is sometimes prescribed in emergencies when there is a serious vaso-occlusive complication or in programmed circumstances to prepare a patient for a surgical operation.
The onset of an acute thoracic syndrome, CVA, priapism or hepatic sequestration are all an indication (Professional Agreement).
This indication may be extended to septic shocks and attacks of pain that resist analgesics.
The risk of infectious or vaso-occlusive post-operative complications is high among sickle-cell patients. the usual practice is to perform a pre-operative exchange transfusion to lower HbS below 30 to 40%. it is recommended to modulate this according to the duration of anaesthesia and the type of operation.

Indications for exchange transfusion in the long term
Exchange transfusion programmes constantly maintaining the level HbS below 30-40% are proposed for some sickle-cell patients: after CVA, in the event of severe visceral damage (respiratory disease, renal or heart failure).

*In pregnant women*, one frequent practice is to transfuse between the 5th and 9th month in order to maintain [Hb] between 10 and 11 $g.dL^{-1}$.

- **Other haemoglobinopathies**

The other haemoglobinopathies only exceptionally cause anaemia requiring RCC transfusions: notably homozygosis for Hb C, E, certain unstable types of Hb.

- **Anomalies of the red cell membrane and red cells enzyme deficiencies**

The vast majority of patients with anomalies of the red cells membrane and red cells enzyme deficiencies (principally G6PD and pyruvate kinase) only receive RH-KELL phenotyped and leukodepleted RCCs when they have episodes of acute reduction of circulating red blood cells. Rare patients (particularly sufferers from pyruvate kinase deficiency) are subjected to iterative transfusion programmes whose conditions are identical to those for patients with thalassaemia.

### 4.3. TRANSFUSION OF RED CELLS DURING CONSTITUTIONAL DISEASES AND CONGENITAL APLASIA

- **During constitutional diseases and congenital medullar aplasia**

These are chronic forms of anaemia in children, usually well tolerated.

Transfusion threshold
Recommended threshold: [Hb] = 7 to 8 $g.dL^{-1}$, according to clinical tolerance. There are no studies defining an optimum threshold. There is no indication regarding hypertransfusion.

Products transfused
- RH-KELL phenotyped leukodepleted RCCs:
The phenotyping of the patient must be as extensive as possible. It must be performed before the first transfusion and the donors must be selected strictly according to this phenotype.
The CMV status of the recipient and donor does not have to be taken into account in non-immunodepressed children, who are protected by leukodepletion of the RCCs. Irradiation is not justified in such non-immunodepressed cases. The

only exceptions are intra-family donation (regulatory obligation) and the period immediately before a haematopoietic stem-cell graft.

♦ **During acquired medullar aplasia**

The RCC transfusion is governed by the same rules as in cases of congenital aplasia.
As cases of post-transfusion GVH have been reported, medullar aplasia is not an indication for irradiation of the RCCs in adults or children. There are however two situations in which irradiation should be considered:

- intensive immunodepressive treatment;
- if a haematopoietic stem-cell graft is scheduled quickly.

### 4.4. TRANSFUSION OF RED CELLS DURING ACQUIRED HAEMOLYTIC ANAEMIA (AHA)

Indications during AHA
- Severe acute forms of AHA or aggravation of chronic forms;
- Severe chronic forms (more rarely).

During AHA, as in all types of anaemia, the transfusion therapy must be based on multiple clinical and biological criteria: Hb concentration, speed of onset of anaemia, patient's age, associated pathologies, possible drug-related aetiology, underlying diseases which may be responsible for the haemolysis and whose treatment may influence the haemolysis, monitoring of development, assessment of the chances of efficacy and dangers of red cell intake. The same applies to the choice of the administration conditions (type of product, quantity, temperature of the products to be administered).

Transfusion threshold
The most important factor is how well the anaemia is tolerated.
Recommended threshold: [Hb] = 8 $g.dL^{-1}$, in cases of poorly tolerated chronic anaemia, which can only be corrected by transfusion. It is possible not to transfuse at lower thresholds, particularly if the type of improvement sought is short-term, spontaneous or secondary to etiological treatment of the AHA.

Products transfused
- leukodepleted RCCs phenotyped in the RH and KELL systems.

The clinician must face to the difficulties in performing the serological investigations and provide appropriate blood products, particularly in cases of AHA with an immunological mechanism. In certain cases, the services of highly-specialized immuno-haematology laboratories are necessary to search for rare red cells products, sometimes on a nationwide scale (national centre of reference for blood groups).

It is usually impossible to transfuse red cells that do not bear antigens recognized by the present auto-antibodies, because they are generally directed against what are known as "public" antigens, present in most of the population. In the event of auto-antibodies with restricted specificity, it is sometimes possible to transfuse red cells without a recognized antigen. In all other cases, the survival of the red cells transfused is short and the effect of the transfusion is mediocre, even though it is not really dangerous, despite *in vitro* demonstration of incompatibility linked to the presence of auto-antibodies. The red cells transfused are usually destroyed by the auto-antibodies at the same speed as those of the patient (and sometimes more quickly).

The major risk is the occurrence of very serious haemolytic transfusion accidents due to non-detection of acquired allo-antibodies masked by the auto-antibodies. Screening for acquired allo-antibodies requires rigorous serological techniques.

♦ **During auto-immune AHA**

Indications during auto-immune AHA
Transfusion is only a temporary replacement solution which cannot be used as the only means of dealing with the threat of anoxia.
Apart from its low efficacy and the short-term nature of its effects, transfusion may be dangerous because it can cause:

- serious immediate haemolysis due to the presence of unknown immune allo-antibodies or delayed haemolysis due to reactivation of the synthesis of undetectable allo-antibodies;

- allo-immunization with serious consequences for the future.

It may also make the situation worse: stimulation of auto-antibody synthesis, modifications of the type of auto-antibodies, whose specificity could become less restricted (although the reverse also occurs), change from an Ig Coombs direct test to Ig + complement.

The risk of non-detection of acquired allo-antibodies and the poor efficacy of transfusions have led certain authors to prohibit any RCC transfusion during auto-immune AHA, unless immediately life-threatening.

Products transfused

Frozen autologous red cells are only used in the event of auto-immune AHA characterized by repeated episodes of haemolysis, separated by periods when the auto-antibodies disappear. During these periods, the patient's red cells may be sampled for cryoconservation, as long as:

- the auto-antibody is strictly specific to a clearly-determined antigen
- these red cells 1) do not bear antigens against which the patient already possesses allo-antibodies that could cause allo-immune haemolysis;
  2) are not liable to cause allo-immunization which could subsequently prove dangerous and compromise future transfusions and obstetric interventions.

The test of compatibility with the recipient's serum is almost always positive. It must be performed at the temperature at which the auto-antibodies detected bind and are active.

Temperature of the RCCs transfused

In the presence of cold agglutinins or biphase antibodies, it is recommended to transfuse the red cells heated to 37°C by means of a system for heating the tubing on the patient's bed. It may be necessary to raise the temperature of the room above the temperature at which the auto-antibodies may be harmful.

Monitoring of the transfusion

It must be monitored very closely. It is prudent to monitor the first ten minutes of the transfusion particularly closely and, if the patient's condition allows it, to use a slow perfusion rate of around 2 $mL.min^{-1}$ during this phase. Biological monitoring ensures efficacy of the transfusion by measurement of Hb in the hour following the end of the transfusion. Subsequent biological monitoring includes in particular thorough and repeated screening for the appearance of allo-antibodies and non-modification of antibody specificity.

Life-threatening emergency situations

The necessary RCCs must be transfused even though not all the results of the examinations are available. Before the transfusion, it is recommended and almost always possible to take the necessary samples for determining the ABO and RH1 (Rh D) blood groups and for all the immunohaematological examinations (particularly for analysis of the auto-antibodies) and to perform the corresponding tests. The life-threatening emergency authorizes RCC transfusion before the results of screening for allo-antibodies, which takes time due to the presence of the circulating auto-antibodies.

♦ **During immuno-allergic AHA linked to medicines, chemical agents, physical agents or venoms**

In the event of drug-related immuno-allergic AHA, the drug must be stopped (which may be difficult in certain patients). Various agents may cause sometimes severe acute anaemia requiring emergency transfusions or even exsanguino-transfusions.

In transfusion terms, the problems are the same as with auto-immune AHA: possible difficulty of grouping and screening for allo-antibodies.

♦ **During paroxysmal nocturnal haemoglobinuria**

It is recommended to use RCC transfusion as little as possible. The RCCs are leukodepleted and phenotyped; they are not deplasmatized, except in the event of transfusional inefficacity possibly caused by complementary intake by transfusion.

## 5. RED CELL TRANSFUSION IN NEONATOLOGY

*The methods for saving homologous blood are dealt with in Chapter 6.*

### 5.1. DIFFERENT TYPES OF RED CELL DONATION

#### ♦ Single donor

The use of a single donor for multiple transfusions has two theoretical advantages: an immunological advantage and an advantage in terms of infection (reduced number of donors).
A bag of RCC is assigned to each child for a period of 42 days. At each transfusion, a small bag is prepared extemporaneously from this RCC by the ETS blood transformation unit ("paediatric preparation" transformation).

#### ♦ Directed donation

Directed donation has not been authorized in France since 4 January 1993, except in cases of therapeutic necessity (exceptional blood groups, particularly complex situations involving anti-red cells immunization).
When parent-child donation is the only possibility, the compatibility of the donor's serum and the child's red cells must be verified. The product to be transfused must be irradiated and deplasmatized in the event of intra-uterine immunization.

#### ♦ Transfusion of RCCs kept for less than 7 days

"Fresh" RCCs have a storage period of less than 7 days. They contain red cells which have not been significantly affected by storage lesions. The fraction of transfused red cells circulating 24 hours after transfusion is high (> 80%) and decreases regularly down to a limit of 70-75%, which determines the length of the storage period.

Indication for transfusion of RCCs kept for less than 7 days (Professional Agreement)
In neonates, as the metabolic modifications caused by storage in terms of the red cells and the plasma may be dangerous, the transfusion of RCCs stored for less than 7 days is recommended in the event of:

- massive transfusion ($\geq$ 1 blood volume) in cases of acute hypovolaemia ;
- exsanguino-transfusion;
- transfusions performed in the context of techniques for purging $CO_2$ from the body.

In all other indications, it is possible to use RCCs stored for more than 7 days without harmful effects in neonates.

### 5.2. INDICATIONS FOR RED CELL TRANSFUSION

#### ♦ Transfusion in the foetus

Intravascular transfusion requires experienced staff, but appears superior to intraperitoneal transfusion, which is only performed when intravascular transfusion is impossible, notably in the very early stages of pregnancy.

Indications in the foetus
- Severe anaemia linked to allo-immunization in the RH system or the other blood group systems.
- Anaemia linked to infection by parvovirus B19 or massive intra-uterine haemorrhage.

They are determined according to the [Hb], the kinetics of its development (in the event of iterative transfusions), the concentration of antibodies present in the foetal blood and the extent of foetal erythroblastosis and reticulocytosis. No studies have validated a threshold above which the benefits of transfusion outweigh its disadvantages.

The aim is to prolong the pregnancy by improving foetal tissular oxygenation.

The indications have to take into account the risks inherent to foetal transfusion:
- risk of foetal intervention, which can be evaluated at between 1 and 3% in terms of lethality;
- risk of reactivating intra-uterine allo-immunization due to foetal vascular access, notably when it is transplacental, as this may lead to communication of the foetal and maternal blood supplies;
- post-transfusion infectious risk for the mother, which may be linked to the injection of red cells in the intervillous spaces of the mother, intra-uterine haemorrhage or intra-amniotic bleeding.

The indication of foetal blood sampling and the date when it is carried are determined on the basis of a range of arguments, including:

- existence or absence of foetal oedema, foeto-placental anasarca or signs of alteration of the foetus's well-being on Doppler ultrasonography scans;
- the $\Delta$ of optical density of bilirubin at 450 nm ($\Delta$OD 450) in the amniotic fluid if it rises rapidly (Liley chart);
- a discrepancy between the serum concentration of maternal allo-antibodies and the results of the $\Delta$OD 450;
- the obstetric history and, in particular, the term at which any complications possibly linked to allo-immunization may have occurred in a previous pregnancy;
- the necessity of determining the foetal blood group (which can also be obtained by PCR on the cells in the amniotic fluid).
- the existence of foetal heart rhythm anomalies pointing to poor tolerance of the anaemia by the foetus.

Transfusion threshold

There are no arguments for giving priority to any of the following transfusion thresholds:

- 10 $g.dL^{-1}$ (or foetal Ht < 30%). This threshold is questionable as it does not take the gestational age into account;
- 7 $g.dL^{-1}$ from the 4th to the 6th month of pregnancy or 9 $g.dL^{-1}$ in the last 3 months;
- - 2 SD in relation to the norms for the gestational age.

Products transfused

The RCCs used are (Professional Agreement):

- less than 5 days old, with a known Hb or Ht content (if possible around 80%);
- group O, free of haemolysin;
- compatibilized with the mother's serum, while imperatively respecting the antigenocompatibility in the RH and KELL systems, and possibly in the other recognized immunogenic systems (Duffy, Kidd, MNS3 (S), MNS4 (s)) ;
- irradiated;
- if possible CMV-negative.

Volume to be transfused

For an intravascular transfusion, the transfusion volume can be determined in theoretical terms by means of the formula:

$$\text{Volume to transfuse (in mL)} = \frac{(\text{[Hb] required} - \text{foetal [Hb]}) \times \text{FPBV}}{(\text{[Hb] of product} - \text{[Hb] required})}$$

FPBV (foeto-placental blood volume) = 90 to 120 $mL.kg^{-1}$ of foetal weight. Pertransfusional determination of [Hb] in the foetal blood is usually carried out when two thirds of the theoretical volume have been transfused.

Ultimate aim: [Hb] = 16 to 17 $g.dL^{-1}$ or foetal Ht = 45 to 50%. Lower values should be aimed for in cases of foeto-placental anasarca. The appropriateness of the volume transfused is assessed from the results of the foetal blood counts performed during transfusion.

There are no objective arguments supporting the recommendation of *in utero* exsanguino-transfusion rather than simple transfusion in an anaemic foetus showing no signs of foeto-placental anasarca. From the foetal viability date, monitoring of foetal well-being is necessary during the hours following *in utero* transfusion.

### ♦ Transfusion in neonates

It is not recommended to transfuse RCCs with the sole purpose of maintaining an Hb concentration (Professional Agreement).

The indication of RCC transfusion depends on:

- the existence of clinical signs of intolerance of the anaemia;
- the pathological context and the associated risk factors;
- the significance of the difference between [Hb] and the reference values for the gestational age and postnatal age;
- the anaemia's speed of onset;
- the possibilities of medullar regeneration.

Studies are required to validate criteria for assessing the severity of anaemia in neonates and the indication of RCC transfusion.

In the event of acute haemorrhage, the intensity and duration of the haemorrhage, the possibilities of treating the cause, the kinetics of the anaemia's development and its effects on tissular oxygenation are better criteria than the isolated Ht or [Hb] value.
A collapse of non-haemorrhagic origin is not a recognized indication for RCC transfusion. Volaemia must be maintained by means of volaemic expansion solutions (Grade A).

In neonates in severe respiratory distress, particularly if they require ventilatory support, the threshold of [Hb] = 12-13 $g.dL^{-1}$ or Ht = 35-40% is usually recommended, although it has the disadvantage of not taking the gestational age into account and it has not been validated by controlled studies (Professional Agreement).

The concept of a transfusion threshold is not defined for premature infants, once the phase of life-threatening complications in the first few days of life is over, or in asymptomatic premature infants. It is proposed to use the following indicative thresholds above which RCC transfusion is *a priori* not indicated:

- 12 $g.dL^{-1}$ during the initial period of intensive care,
- 10 $g.dL^{-1}$ during the period following the first 2 weeks of life,
- 7 $g.dL^{-1}$ and a reticulocyte concentration of 100,000 $mm^{-3}$, subsequently.

### ♦ Exsanguino-transfusion in neonates

Indications for exsanguino-transfusion
- Haemolytic disease, with the aim of extracting immune antibodies directed against the neonate's red cells, purging the free bilirubin and correcting the anaemia. Its objective is to avoid kernicterus and the other forms of bilirubin neurotoxicity. Exsanguino-transfusion improves the survival rate of children presenting intra-uterine RH allo-immunization (Grade B).
- Other indications have been proposed: disseminated intravascular coagulation (DIVC) certain innate metabolic defects revealed in neonates. Optimum treatment of the causes of DIVC tends to make the indications disappear. The treatment of innate metabolic defects is turning to haemodiafiltration techniques.

Exsanguino-transfusion threshold
The indication threshold rises progressively with the postnatal age until the 3rd day of life. It is lower in premature infants or neonates with low birth weight, or when there are or have been conditions liable to alter the immature haemato-encephalic barrier, such as acute foetal distress or metabolic acidosis.

In the event of neonatal haemolytic disease, different thresholds are proposed (Grade C):
- 340 to 430 $\mu mol.L^{-1}$ of total bilirubin in full-term neonates with RH immunization, from the 3rd day,
- up to 540 $\mu mol.L^{-1}$ in the forms of jaundice observed in healthy full-term neonates, with no RH immunization.

Alternatives
Phototherapy is the first-line treatment in cases of neonatal hyperbilirubinaemia. It often allows exsanguino-transfusion to be avoided when it is intensive. In cases of intra-uterine allo-immunization, *in utero* transfusions tend to reduce the indications of exsanguino-transfusion.

Products transfused
- Whole blood or blood reconstituted from RCCs stored for less than 5 days and from FFP. There has been no proof of greater transfusional efficacy using products stored for less than 3 days.
it is recommended to use RCCs:
  - of a blood group compatible with both the neonate's and the mother's;
  - RH-KELL phenotyped;
  - irradiated (necessary in premature neonates and recommended in full-term neonates).

Deplasmatization of the RCCs could represent an alternative to the use of RCCs stored for less than 7 days, particularly in terms of the risks attributed to the storage solution.
The use of human albumin in place of the FFP to reconstitute the blood has been proposed. But no studies are available which establish its tolerance and efficacy in terms of buffering capability and blood coagulation.
The volume exchanged is $\geq$ 2 fold the child's total blood volume. Neonate volaemia is usually 80 $mL.kg^{-1}$.

## 6. ALTERNATIVES TO HOMOLOGOUS TRANSFUSION

The measures for reducing homologous blood transfusion include autologous transfusion and recombinant human erythropoietin (EPO). The problem lies in defining the appropriate indications for these. It is currently considered that the indications are based on defining individual transfusion requirements as precisely as possible.

### 6.1. AUTOLOGOUS TRANSFUSION

#### ♦ Programmed autologous transfusion (PAT)

The efficacy of the method for avoiding homologous transfusion is recognized. PAT may be considered in any person weighing more than 10 kg and requiring a scheduled haemorrhagic operation in the absence of contra-indications (Grade A). The contra-indications are:

- those exposing the patient to a risk:
  - [Hb] < 11 $g.dL^{-1}$ or Ht < 33% (contra-indication for initiation or continuation of the programme),
  - any latent or overt infectious pathology (urinary, digestive, dental, other),
  - patients who are long-term wearers of urinary catheters,
  - cardiac pathology, and particularly:
    - unstable angina,
    - angina attack in the previous 8 days,
    - extreme aortal narrowing,
    - cyanogenic cardiopathy,
  - severe occlusive cerebral arteriopathy;
- those involving a collective risk: subjects who are carriers of direct viral markers, due to the risk of contaminating another patient in the event of incorrect product assignment;
- refusal by the patient for personal or religious reasons.

*In children*: PAT is difficult to perform under 15-20 kg because of vein access difficulties.

*In pregnant women*:: the indications are rare and difficult to foresee. Peripartum haemorrhages often require several RCCs, so homologous transfusion of complements is usually necessary. The indication should be considered in cases of total placenta accreta or praevia, with a rare blood group, involving allo-immunization and foeto-maternal incompatibility.

*During elective surgery,* PAT may be scheduled 3 to 6 weeks in advance, when the expected blood loss exceeds 1,000 to 1,500 mL, such as in: orthopaedic surgery (hip, knee, extensive spinal surgery), cardiac surgery, major vascular surgery. Carcinological surgery is not a contra-indication.

Due to the multiple determinants regarding blood loss, it is essential for each unit to assess the transfusion requirements specific to each type of routine surgery practised, in order to adapt the indication for PAT and the amount of autologous RCCs necessary for it.

The situations modifying the benefit/risk ratio of PAT must be the subject of concertation between the medical partners (anaesthetist-resuscitator, haemobiologist, surgeon):

- the expected benefit is usually only significant if life expectancy is $\geq$ 10 years;
- specific homologous transfusion problems may increase the benefit/risk ratio (availability of compatible homologous blood in a rare blood group system, risk of transfusional allo-immunization).

PAT does not eliminate the possible necessity of homologous transfusion. It cannot and must not be presented to the patient either as a guarantee of non-exposure to homologous LBPs or as free of any transfusion-related risks (particularly bacterial contamination).
The samples are taken in successive donations several weeks apart or in a single donation by erythrocytapheresis.
Iron supplementation must be given in cases of PAT.

#### ♦ Autologous transfusion by intentional normo-volaemic haemodilution

Compared with simple passive haemodilution, the homologous blood saving promised by this technique is, at best, modest in return for a significant reduction in haemoglobinaemia. There has been insufficient validation of its efficacy, except in cardiac surgery. It cannot therefore be considered an alternative to PAT.

Its use alongside other techniques may be considered particularly in haemorrhagic surgery. It is not indicated in surgery causing moderate bleeding (< 50% of the blood volume), except in special cases (rare blood groups, transfusional allo-immunization). It requires vigilance, experience and knowledge of the physiological disturbances and risks inherent to profound haemodilution.
It is contra-indicated in patients with reduced tolerance of haemoglobinaemia. Continuous monitoring of $S\overline{v}O_2$ is recommended in the event of profound haemodilution.

♦ **Autologous transfusion by peri-operative recovery**

- Peri-operative recovery

This technique appears particularly justified if the surgery is haemorrhagic and it is impossible to carry out a PAT programme or the programme does not allow self-sufficiency. Its best indications are in cardiac and vascular surgery (Professional Agreement). Its use in neoplasic surgery and in obstetrics is currently a subject of debate.
It is contra-indicated in cases involving infected surgical sites or the use of biological glues.
Retransfusion of large amounts of blood gathered in the surgical wound and not washed may lead to complications. The maximum tolerable volumes of unwashed blood are impossible to specify because they necessarily vary according to the type of surgery and bleeding. The technique appears safe for volumes that do not exceed 1,000 mL. Retransfusion of larger volumes requires washing.
The use of simple systems for blood recovery without washing in pre-hospital resuscitation of patients suffering from traumatic haemothorax is a documented rescue technique.

- Post-operative recovery

Post-operative autologous transfusion may be performed in prosthetic knee surgery with a tourniquet, notably when PAT is impossible (Professional Agreement). Its efficacy in prosthetic hip surgery has not been established. Its usefulness in cardiac surgery merits re-assessment. Its usefulness must be assessed according to the post-operative blood loss usually observed in each centre.
This technique is contra-indicated in the event of local or general infection or renal disease.
The blood recovery period must be limited to the first 6 hours following the operation.

♦ **Use of autologous placental blood in neonatology**

- Delayed clamping of the umbilical cord in premature neonates at birth

Delayed clamping of the umbilical cord enables placental blood to be recovered and thus increase the blood mass by 30 to 50%. The optimum conditions for performing this, notably in terms of the duration of the delay and the child's position, as well as tolerance of the volaemic modifications caused are currently being studied. This simple method of reducing transfusion should not postpone the implementation of resuscitation procedures when they are indicated and required in all cases close monitoring of the neonate during the placento-neonatal transfusion.

- Transfusion using autologous placental blood

Recovery of autologous placental blood from the umbilical cord (for possible subsequent transfusion), with the aim of reducing transfusion risks in premature neonates during the first month of life, is currently being studied. Feasibility of this method depends on the possibilities of mobilizing the necessary personnel at the time of birth. The risk of septic contamination currently observed indicates that additional studies are required to improve the quality of the recovery and storage of the placental blood.

### 6.2. ERYTHROPOIETIN (except in cases of chronic renal disease)

♦ **Use during malignant haemopathies and in oncology**

Erythropoietin (EPO) may correct cancer-related anaemia and malignant haemopathies, whether treated by chemotherapy or not, removing or significantly reducing the red cells transfusion requirements. It is recommended to use it when the risk of severe anaemia is high and the probability of a response to EPO is strong (Grade A).
The risk of onset of severe anaemia during chemotherapy is even greater if the patient is already anaemic, lymphopaenic and suffering from an alteration of general health. Response to the treatment is more probable if the serum EPO concentration is low, the patient has a myeloma or the patient is receiving treatment with cisplatin.

The minimum time for obtaining an initial response is around 2 to 3 weeks; it is longer in the event of an inflammatory syndrome. As anaemia rapidly alters quality of life, instead of applying the classic transfusional approach, which is usually prudent and delayed, it is advisable to begin EPO treatment in the initial stages of anaemia, if this treatment is chosen.

- **Use in the context of PAT**

In the context of PAT, the documented indications of EPO are those with the AMM label, combined with oral or intravenous iron supplementation (Grade A).

- **Peri-operative use outside PAT**

In moderately anaemic patients (10 < [Hb] < 13 $g.dL^{-1}$), EPO reduces homologous transfusion during operations causing blood loss of around 1,000 mL. It is essential to associate this with oral or intravenous iron supplementation. In Europe, the AMM of EPO outside PAT is limited to orthopaedic surgery only. There are no scientific arguments that exclude scheduled surgery causing similar foreseeable blood loss.
The risk of arterial thrombosis has been mentioned in patients undergoing coronary artery bypass surgery. The serious vascular situation is a contra-indication for EPO treatment when it is not associated with PAT.

- **Use in neonatology**

EPO helps to reduce the frequency and volume of transfusions in premature neonates.
However, it does not allow transfusions of certain extremely premature neonates to be avoided during the first weeks of life, because of its delayed action. Its benefit may be reduced in the event of a restrictive transfusional indication and in cases where a single donor is used for repeated transfusions. It is recommended in the prevention of anaemia in premature neonates (Professional Agreement), mainly if the birth weight is < 1,000 g or the gestational age is < 34 weeks, in the following conditions:

- early administration (start between the 3rd and 8th day), because the effect of EPO on [Hb] requires at least 15 days to occur;
- a dose of approximately 750 U/kg/week, spread over 3 sub-cutaneous administrations[2] ;
- early enteral iron supplementation, beginning at 2 $mL.kg^{-1}.d^{-1}$ of elemental iron, and rising to 6 to 8 $mL.kg^{-1}.d^{1}$ after 15 days of EPO treatment if digestive tolerance allows it.

However, new studies are required to evaluate the reduction in the number of donors after treatment with EPO.

- **Postpartum anaemia**

The use of EPO in the treatment of peripartum and postpartum anaemia is currently a subject of debate. In the light of the contradictory results yielded by the studies, its use cannot be recommended.

### 6.3. IRON

Every time surgery expected to be haemorrhagic is scheduled, it is advisable to precede this with oral martial treatment for a period of several weeks, when possible. Oral martial treatment remains the treatment of reference and first intention for moderate peripartum and postpartum anaemia.

The usefulness and conditions of martial treatment by post-operative and postpartum intravenous perfusion remain to be defined. Preliminary data appears encouraging, but there are no studies comparing it with oral administration. It is recommended to carry out this type of study. Failure or poor observance of the oral martial therapy, major digestive intolerance of orally-administered iron salts or situations involving iron malabsorption are the only recognized uses of intravenous iron-sucrose preparations (Professional Agreement).

[2] The use of intravenous EPO has been adopted by a number of professionals for the prevention of anaemia in premature neonates.

### 6.4. OXYGEN CARRIERS

No oxygen carriers, whether haemoglobin solutions or fluorocarbons, are currently commercialized.

## APPENDICES

**APPENDIX I: PRINCIPAL CHARACTERISTICS OF RED CELLS PRODUCTS AND THEIR TRANSFORMATIONS**

**APPENDIX II: LIST OF BLOOD GROUP ANTIGENS**

**APPENDIX III: GENERAL ORGANIZATION OF EMERGENCY TRANSFUSION**

## APPENDIX I

### PRINCIPAL CHARACTERISTICS OF RED CELLS PRODUCTS AND THEIR TRANSFORMATIONS

| Product | Type of transformation | Haemoglobin content per product (g) | | | Volume (mL) | | | Storage duration (days) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Closed system with adenine | | Open system |
| | | Min | Ave | Max | Min | Ave | Max | Yes | No | |
| Leukodepleted whole blood | | 40[a] | - | - | 350 | - | 563 | 7 | 7 | |
| Leukodepleted SAGM[b] RCC AU | | 40[c] | 54 | 70 | 225 | 284 | 400 | 42 | | 1 |
| Leukodepleted SAGM[b] RCC AU | Deplasmatized | 35[d] | 51 | 66 | | | | | | 6 hours |
| Leukodepleted SAGM[b] RCC AU | Cryoconserved | 35 | 43 | 50 | | | | 7[e] | | 1 |
| Leukodepleted SAGM[b] RCC AU | Irradiated | 40 | 54 | 70 | 230 | 280 | 410 | 42/1[f] | | |
| Leukodepleted SAGM[b] RCC AU | Volume reduction | 40 | 54 | 70 | 175 | | | | | 1 |
| Leukodepleted SAGM[b] RCC AU | Reconstituted blood | 40 | 54 | 70 | 320 | | | | | 1 |
| Leukodepleted SAGM[b] RCC AU | Paediatric preparation | | | | 50[g] | | | 42 | | 1 |
| Leukodepleted whole blood CU | | 22[a] | - | <40 | 283 | | 333 | 7 | 7 | |
| Leukodepleted RCC CU | | 22[a] | - | <40 | 85 | | 240 | 35 | 21 | |
| Leukodepleted SAGM RCC CU | | 22[a] | - | <40 | 155 | | 340 | 42 | | |

*a: regulatory values; LBP very rarely used*
*b: from whole blood or apheresis*
*c: data from the national LBP quality control database*
*d: data from an EFS unit (2001)*
*e: after thawing and placing in a conservation solution*
*f: 42 days after sampling, if irradiation is performed before the 15th day of storage;*
*24 hours after irradiation, if it is performed from the 15th day of storage onwards.*
*g: each transformed RCC gives rise to the several paediatric preparations (minimum 4, maximum 8.)*

## APPENDIX II

### LIST OF BLOOD GROUP ANTIGENS

For naming of the phenotype, the symbol of the blood group system is followed by a colon and the numbers representing the specificities are separated by commas. Positive results are not indicated; negative results are indicated by putting a minus sign before the number. There is no space between each number. For example:

- the phenotype RHD+C+E-c+e+,Cw- is written as RH: 1,2,-3,4,5,-8.

- The phenotype KELL K-k+, Kp(a+b-) is written as KEL: -1,2,3,-4.

For written and verbal use of antigen designation, the number of the blood group system and zero placed to the left of the antigen number can be eliminated and there is no space between the system symbol and the number. For example RH1, RH46, KEL3.

The designation of an antibody's specificities includes the word "anti" followed by a hyphen, the alphabetical symbol of the system and the number of the antigen, without spaces between each sign. For example, anti-E is written anti-RH3.

For the symbols of genes and haplotypes, the characters are in italics. When italics cannot be used, the symbol of the blood group system must be underlined. For example, *R1/R1, DCe/DCe* (R1/R1, DCe/DCe) becomes *RH: 1,2,5/1,2,5* (RH: 1,2,5/1,2,5).

| **Correspondence of naming systems** | |
|---|---|
| **Rhesus system antigens** | |
| D | RH1 |
| C | RH2 |
| E | RH3 |
| c | RH4 |
| e | RH5 |
| **KELL system antigens** | |
| K | KEL1 |
| k | KEL2 |
| **Duffy system antigens** | |
| $Fy^a$ | FY1 |
| $Fy^b$ | FY2 |
| **Kidd system antigens** | |
| $Jk^a$ | JK1 |
| $Jk^b$ | JK2 |
| **MNS system antigens** | |
| M | MNS1 |
| N | MNS2 |
| S | MNS3 |
| s | MNS4 |
| **P system antigens** | |
| P1 | P1 |
| **Lewis system antigens** | |
| $Le^a$ | LE1 |
| $Le^b$ | LE2 |

## APPENDIX III

### GENERAL ORGANIZATION OF EMERGENCY TRANSFUSION[3]

Health-care institutions and transfusion sites should specify the necessary set-up to deal with emergencies in the best possible way. It is up to:

- The health-care institutions to organize matters so that they:
  - Have the results at the right time
  - Warn the transfusion site of the emergency: immediate life-threatening emergency, life-threatening emergency or "relative" emergency, so that all the procedures can be implemented immediately.
  - Warn the transfusion site in SIA-positive cases, so that compatible blood products can be prepared as quickly as possible.
  - Track down false identities and indicate spelling corrections.

- The transfusion sites to organize matters so that they:
  - Recognize LBP prescriptions linked to an immediate life-threatening emergency, a life-threatening emergency or a "relative" emergency and respond to it by appropriate distribution: immediate, deferred or precautionary transfer to the blood bank.
  - Begin the immuno-haematological examinations as soon as the specimens are received, communicating the biological results to the prescribing physician as soon as possible.
  - Take into account SIA-negative results from laboratories other than the distributing site's laboratory (if the analysis has been carried out according to the regulatory criteria).

- Both the health-care institution and the transfusion site to:
  - Analyze in each region the meshing between emergency services and transfusion sites so that RCC is available within 30 minutes, "all year round, 24 hours a day". To obtain RCC in the context of a life-threatening or immediately life-threatening emergency (in under 30 minutes), there are three possible solutions: there is an EFS transfusion site nearby, a blood bank with allocation authorization is located in the health-care institution or there is a vital emergency bank in the institution governed by strictly regulated conditions.
  - Establish the quantity and quality of vital emergency stocks. The stock should voluntarily be kept small (its purpose is to ensure survival of the patient during the time necessary for supply of other RCCs); it is advisable for it to be made up of only 2 RCCs O RH : -1,-2,-3 KEL: -1 (formerly ccddee K-) and 2 RCCs O RH: 1.2,-3,-4.5 KEL: -1 (formerly CCDee K-).
  - With all the people involved, draw up vital emergency prescription procedures at both the health-care institution and the transfusion site and ensure that they operate correctly. Aspects to be clarified include all the conditions for communication between the health-care institutions and the transfusion sites.
  - Plan replenishment of the emergency blood bank.
  - Organize transportation in accordance with good transport practices for specimens, products and samples derived from human blood, specifying (regulatory obligation): - who provides the examinations, - who transports the blood, - with what lead time (definition of minimum lead time for obtaining blood products, including transport time and unavoidable distribution time, according to the examinations necessary), - the opening hours, - the means of transport (type of vehicle and containers, temperature control methods, etc.), - who replenishes the blood bank and in what conditions… Precise specifications must be drawn up and a contract must clearly define the different aspects of the transport between: the health-care institution, the transfusion site and the carrier.
  - The assessment of the measures implemented must be clearly defined in a schedule: weekly at first, then monthly and finally quarterly, drawn up by the health-care institution and the transfusion site.
  - It is recommended to include any written trace of any events in the clinical file, to assist subsequent enquiries and assessments.

[3] According to the conclusions of the round table organized by the EFS on the treatment of obstetrical transfusional emergencies.

**Life-threatening emergency procedure**

**Determine the indication of transfusion**

↓

Write the LBP prescription

↓

Warn the transfusion site of the degree of urgency: immediate life-threatening emergency or life-threatening emergency (Tel. , fax accessible 2' hours a day)

↓

Notify the 24/7 means of transport (internal or external to the institution)

↓

Transmit the prescription + the documents to the transfusion site or the blood bank (fax, etc.)
+/- the necessary specimens

***Distribute the LBPs immediately (or organize immediate distribution)***

| **Complete IH documents available** | | **Incomplete IH documents available (1 group determination only, SIA > 3d)** | **Absence of IH documents** |
|---|---|---|---|
| ***Iso-group blood if immediately available*** | ***If not,*** 2 RCCs O* free of haemolysin<br>☞continue with compatible RCCs | ***2 RCCs O**** free of haemolysin<br>• sample for SIA<br>• sample for 2nd group determination if necessary<br>• ☞ continue according to result | ***2 RCCs O**** free of haemolysin<br>• sample for SIA + blood group with RH-KELL phenotype<br>• sample in a different sequence for 2nd group determination<br>• ☞ continue according to these last results |

Notify the immuno-haematology laboratory (tel. , fax 24 hours a day)

↓

Receive the LBPs, check the documents (if available) + last bedside check on patient and transfusion of the LBPs (inform the patient if he/she is sufficiently conscious)

↓

Notify the transfusion site or the blood bank of the subsequent LBP requirements

↓

Traceability + Regular evaluation of the procedure

***either RH: -1, KEL: -1, or RH: 1 (RH: -3,-4), KEL: -1 (formerly: either RH neg, KELL neg, or RH pos (E-, c-) KELL neg)***