Recommendations for the transfusion management of patients in the peri-operative period. III. The post-operative period.

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Aetiology and prevention of anaemia

Prevalence of anaemia

Various studies have documented the high prevalence of anaemia and the frequent use of transfusions of allogeneic blood and blood components in the post-operative period[1-5]. In a prospective, observational, multicentre study carried out in Europe in 1999 on 3,534 patients admitted to intensive care units [ABC (Anaemia and Blood Transfusion in Critical Care) study][6], the mean level of haemoglobin (Hb) on admission was 113±23 g/L and 29% of the patients had a Hb concentration below 100 g/L. The overall rate of transfusions during the admissions was 37%, being higher in patients admitted because of surgical emergencies (57.5%) than in those admitted because of trauma (48%), elective surgery (42.1%), or medical causes (32%)[6]. Similar results were found in an analogous study (CRIT study) carried out in the USA in 2000 on 4,892 patients: the mean level of Hb at admission was 110±24 g/L, and the overall rate of transfusion was 44%[7]. A large, multicentre study in Scotland in 2003 showed that at the time of discharge from the intensive care units just under 90% of the patients were anaemic (Hb <130 g/L in males and <115 g/L in females) and about 50% had a Hb concentration below 100 g/L[8].

The impact of anaemia in patients during the post-operative period and its optimal treatment have not been clearly deÞned and there are no universally accepted "transfusion thresholds". In these patients, many transfusions are probably carried out on the basis of arbitrary choices, rather than on real clinical needs[9].

Aetiology of anaemia

Post-operative anaemia may be caused by various factors: acute or chronic blood loss, reduced erythropoiesis, shortened red blood cell survival (Table I)[10,11].

Surgical bleeding plays a key role and is related to the type of operation. The ABC study showed that the mean levels of Hb on admission to intensive care units were lower in patients who had undergone emergency surgery (108 g/L) than in those who had undergone elective surgery (110 g/L) or trauma (115 g/L) or who had medical disorders (119 g/L). Post-operative blood losses can be signiÞcant, particularly in cases of cardiovascular and orthopaedic surgery[6,12-16].

Repeated sampling of blood to carry out laboratory

Table I - Possible causes of surgery-related anaemia in the post-operative period.

Acute or chronic blood loss
- Intra-operative or post-operative bleeding
- Repeated blood sampling
- Gastrointestinal bleeding
Reduced erythropoiesis
- Reduced production of erythropoietin
- Resistance to the action of erythropoietin
- Reduced ability to use iron
Shortened red blood cell survival

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tests is a relevant cause of anaemia. It is estimated that, in the absence of speciÞc measures, the mean daily blood loss per patient is about 40 mL and that up to 30% of transfusions given in intensive care units are due to this cause[1,6,10,11,17,18].

Gastrointestinal bleeding, secondary to stress-related mucosal disease, is another possible cause of anaemia, even though its contribution is probably overestimated. Such bleeding has many underlying mechanisms, which are not completely understood, and occurs in 0.2-6% of patients admitted to intensive care units. SpeciÞc risk factors are respiratory failure requiring ventilatory assistance, clotting disorders, acute renal failure, acute liver failure, sepsis, a history of gastrointestinal bleeding, and administration of high doses of corticosteroids[2,19-22].

Coagulation disorders, such as thrombocytopenia, platelet function defects, clotting factor deÞciencies and hyperÞbrinolysis, are present in many critically ill patients in the post-operative period and can worsen acute and chronic blood loss[11,23].

Reduced erythropoiesis in critically ill patients has been reported in different studies and could be caused by various factors related to the inßammatory state. High concentrations of inßammatory cytokines, such as tumour necrosis factor-α, interleukin-1 and interleukin-6, are often present in patients with sepsis or patients who have undergone trauma and can cause a reduction in the production of erythropoietin or inhibit erythropoiesis even in the presence of normal circulating concentrations of this hormone[10,11,24-29].

The acute phase inflammatory response can also modify iron metabolism and compromise the optimal use of this element by the bone marrow, leading to inadequate erythropoiesis for the degree of anaemia[10,11,30-32].

Shortened erythrocyte survival can contribute to the anaemia that occurs in the post-operative period in some critically ill patients. The use of cardiopulmonary bypass for heart surgery and valve replacements can both lead to a variable degree of haemolysis. Some procedures, particularly those that cause tissue damage, induce oxidative stress with release of radicals capable of compromising the integrity of the red cell membrane. Premature destruction of red blood cells can occur in critically ill patients with systemic inßammatory response syndrome (SIRS) or sepsis because of the activation of complement. There is no evidence of shortened erythrocyte survival in other situations[10,11,33,34].

Table II - Strategies that can be used to reduce the need for blood transfusions.

- Constant monitoring of the critically ill patient
- Prophylaxis against gastrointestinal bleeding
- Limitation of iatrogenic blood losses
- Optimisation of oxygen release to tissues
- Containment of oxygen consumption by tissues
- Optimisation of erythropoiesis

Prevention of anaemia

The expansion of plasma volume following administration of fluids can simulate a state of anaemia and, when evaluating the patient's clinical and biological parameters, the two conditions should be differentiated (*Grade of recommendation:* 1C+)[10].

The strategies that can be used to prevent anaemia and, thereby, reduce the need for transfusion of allogeneic blood components, are listed in Table II[10,35-37].

Constant monitoring of the critically ill patient is of help in preventing bleeding and treating episodes of haemorrhage. The Þrst measure consists in promptly identifying and treating any clotting disorders. Bleeding must be treated rapidly, before the patient's physiological reserves are excessively reduced. Appropriate surgical interventions can be used in the presence of localised bleeding (*Grade of recommendation:* 2C); angiographically guided embolisation can be a useful strategy[35-37].

In the case of uncontrolled bleeding, a state of mild or moderate hypotension can be established through restriction of infused ßuids; the blood pressure must be controlled very carefully and restored to normal values as soon as the bleeding is halted (*Grade of recommendation:* 2C)[35-37].

When the bleeding is generalised or its site cannot be reached, the use of haemostatic agents such as tranexamic acid should be considered (*Grade of recommendation:* 2C+)[38-42].

Prophylaxis against gastrointestinal bleeding, with antacids, sucralfate, H_2 receptor antagonists, or pump inhibitors, is justiÞed in patients at the highest risk, in particular those undergoing mechanical ventilation for more than 48 hours and those with altered blood

coagulation; at present there is no evidence in favour of the routine use of these drugs in all patients in the post-operative period (*Grade of recommendation:* 1C+)[43-48].

The aim of minimising iatrogenic blood loss should be pursued by only carrying out essential laboratory tests, withdrawing only the strictly necessary amount of blood, performing multiple tests on a single blood sample, using devices to minimise unnecessary blood losses and implementing speciÞc guidelines (*Grade of recommendation:* 2C+)[2,9,49-52].

Optimisation of oxygen release to the tissues can be favoured by the maintenance of an adequate cardiac output and the use of oxygen therapy. Limiting oxygen consumption by tissues can be achieved, when required, by using analgesics, sedatives, muscle relaxants and mechanical ventilation; induction of mild or moderate hypothermia may sometimes be appropriate, in the absence of coagulation disorders (*Grade of recommendation:* 2C)[36,53].

Optimisation of erythropoiesis can be pursued by using iron and erythropoietin. Few studies have evaluated the use of iron without associated erythropoietin in the post-operative period. Overall, the beneÞt appears modest; based on results from observational studies, intravenously administered iron can reduce transfusion requirements in patients undergoing orthopaedic surgery, but not in those undergoing cardiovascular surgery[54,55].

In contrast, numerous studies have evaluated the use of iron in combination with erythropoietin. In one randomised study of 1,303 patients, erythropoietin (40,000 UI subcutaneously, once a week, for three consecutive administrations) in combination with iron (150 mg of elemental iron each day, administered orally or parenterally) led to a signiÞcant reduction in transfusion needs, without exposing the patients to the risk of severe adverse reactions, such as thromboembolic complications, allergies, or pure red cell aplasia. These results have been conÞrmed by numerous subsequent studies[10,11,24,29,56-61]. Although it has been clearly demonstrated that erythropoietin can reduce transfusion needs in critically ill patients, it remains to be demonstrated whether this has a clinical beneÞt, in particular in terms of reducing mortality, morbidity and duration of admission, and whether it decreases costs. Consequently, erythropoietin can be used in subjects who refuse transfusion or in selected patients, such as those with complex immunohaematological problems, with renal failure or chronic anaemia, perhaps combined with oral or parenteral iron therapy (*Grade of recommendation* 2C+)[29,56-61]. However, prescriptions of erythropoietin α, β and z are currently paid for by the National Health Service only if the hormone is used to increase the amount of autologous blood in the setting of predeposit programmes, with the limitations set out in the product summary leaßet. In addition to erythropoietin α, β and z, darbepoetin α can also be prescribed for the treatment of anaemia in patients with chronic renal failure. Further studies are necessary to evaluate the usefulness of routine administration of erythropoietin to all patients in the post-operative period.

Transfusion therapy

Post-operative transfusion support is aimed at correcting anaemia and treating secondary coagulation disorders, through the use of the following blood components: allogeneic red cell concentrates (RCC), autologous whole blood or blood components, platelet concentrates and fresh-frozen plasma (FFP)[62-66].

Blood components that can be used

As a guide, one unit of RCC increases the Hb by 10 g/L and the haematocrit (Htc) by about 3% in adults; in children, the transfusion of 5 mL/kg leads to an increase in the Hb of about 10 g/dL. If the increases are less than expected, the presence of detrimental conditions, such as continued blood loss or sequestration or destruction of red blood cells, must be evaluated[66,67].

Autologous blood comprises units of whole blood or RCC obtained by pre-operative donation of autologous blood, acute normovolaemic haemodilution, intra-operative blood salvage or post-operative blood salvage (POBS).

Platelet concentrates can be obtained from a donation of whole blood or by apheresis. The initial dose to be transfused can be calculated using appropriate formulae; it is essential to monitor the efÞcacy of the transfusion in order to have a guide for possible subsequent platelet transfusions[66,68].

FFP can be obtained from units of whole blood or collected by apheresis, The recommended initial dose of FFP is 10-15 mL/kg of body weight. Subsequent

doses depend on the patient's clinical condition, as determined by regular monitoring, and laboratory results[66,68].

Transfusion practice

The pathophysiological mechanisms underlying the need for transfusion of red blood cells, as well as the clinical, instrumental and laboratory parameters, have already been described in the recommendations on intra-operative transfusion (Blood Transfus 2011;**9**:189-217). Also in the post-operative period, the indication for transfusion of red blood cells and the urgency of the transfusion must be determined based on a complete evaluation of the patient's clinical condition (Table III), an assessment of the dynamics of haematological parameters (Hb and Htc) and laboratory and instrumental parameters indicative of inadequate perfusion and oxygenation of vital organs (Table IV)[62,66,67,69-80].

Table III - Clinical parameters to evaluate for transfusion purposes.

Age	Cardiac function
Signs and symptoms of anaemia	Lung function
Speed of blood loss	Ischaemic heart disease
Amount of blood loss	Drug treatments

Table IV - Clinical and instrumental parameters indicative of hypoxia in the anaemic, normovolaemic patient in the post-operative period.

Cardiopulmonary symptoms
- Tachycardia
- Hypotension
- Acute hypotension of unknown origin
- Dyspnoea
Electrocardiographic signs typical of ischaemia
- Newly occurring ST segment elevation or depression
- Onset of arrhythmias
- Newly occurring localised altered contractility of the myocardium
Global indices of insufficient O_2 release, evaluated by invasive methods
- Increase in overall O_2 extraction greater than 50%
- Reduction of O_2 uptake by more than 10% of the initial value
- Reduction of mixed venous O_2 saturation to below 50%
- Reduction of peripheral mixed venous pO_2 to below 32 mmHg
- Reduction of central venous O_2 saturation to below 60%
- Lactate acidosis (lactates >2 mmol/L + acidosis)

Transfusion of autologous whole blood or red cell concentrates

In the presence of acute anaemia, the main therapeutic strategy is to prevent or correct hypovolaemic shock by infusing sufficient amounts of crystalloids/colloids to maintain the blood flow and pressure. The characteristics of the crystalloid and colloid solutions to transfuse and their mode of use have already been described in the recommendations on intra-operative transfusion (Blood Transfus 2011;**9**:189-217) (*Grade of recommendation: 1A*)[66].

The decision to transfuse RCC or whole blood depends on the amount of the blood loss, the Hb concentration and the patient's clinical condition (tables V and VI).

A loss of less than 15% of the blood volume does not usually produce symptoms or require transfusion, providing there is not pre-existing anaemia (*Grade of recommendation: 1C+*)[36-38,62,66,67,75,81-90].

When there is a loss of between 15% and 30% of the blood volume, compensatory tachycardia occurs and the transfusion of RCC is indicated only in the presence of pre-existing anaemia or concomitant cardiopulmonary disease (*Grade of recommendation: 1C+*)[36-38,62,66,67,75,81-90].

Blood losses of more than 30% can cause shock and, when the blood loss exceeds 40%, the shock becomes severe. The probability of having to use transfusion therapy with RCC increases notably with losses of 30-40%, even though volume replacement alone may be sufficient in previously healthy subjects (*Grade of recommendation: 1C+*)[36-38,62,66,67,75,81-90].

Transfusion becomes a life-saving therapy when more than 40% of the patient's blood is lost (Table V) (*Grade of recommendation: 1C+*)[36-38,62,66,67,75,81-90].

Patients with Hb values below 60 g/L almost always require transfusion therapy. In stable patients with Hb values between 60 and 100 g/L, an evaluation of the patients' clinical status is necessary, while patients with values over 100 g/L very rarely need transfusion (*Grade of recommendation: 1C+*)[36-38,62,66,67,75,81-92].

It should be remembered that patients with acute bleeding can have normal, or even raised, values of Htc, until the plasma volume is restored; the clinical evaluation of the patient in this situation is, therefore, extremely important (Table VI) (*Grade of recommendation: 2C+*)[36-38,62,66,67,75,81-92].

In anaemic patients who do not have ongoing

Table V - Decision criteria for the transfusion of patients with acute post-operative anaemia: reduction of volaemia

Class of haemorrhage	Reduction of volaemia (%)	Blood loss (mL)*	Indication for transfusion of RCC	GoR
Class I	<15%	<750	Not necessary, unless pre-existing anaemia	1C+
Class II	15-30%	750-1,500	Not necessary, unless pre-existing anaemia and/or cardiopulmonary disease	1C+
Class III	30-40%	1,500-2,000	Probably necessary	1C+
Class IV	>40%	>2,000	Necessary	1C+

Legend:
RCC: red cell concentrate; GoR: Grade of recommendation; *: in an adult weighing 70 kg with an intravascular blood volume of 5,000 mL.

Table VI - Decision criteria for the transfusion of patients with acute post-operative anaemia

Hb value	Presence of risk factors/mechanisms of compensation	TT with RCC	GoR
≤60 g/L	TT is almost always necessary*	YES*	1C+
60-80 g/L	Absence of risk factors/adequate mechanisms of compensation	NO	1C+
	Presence of risk factors (e.g. coronary artery disease, heart failure, cerebrovascular disease/ limited mechanisms of compensation)	YES	1C+
	Presence of symptoms indicative of hypoxia (physiological transfusion triggers: tachycardia, hypotension, electrocardiographic signs of ischaemia, lactic acidosis, etc.)	YES	1C+
80-100 g/L	Presence of symptoms indicative of hypoxia (physiological transfusion triggers: tachycardia, hypotension, electrocardiographic signs of ischaemia, lactic acidosis, etc.)	YES	2C
>100 g/L	TT is very rarely needed**	NO**	1A

Notes:
- The Hb value is not an adequate indicator of a person's capacity to release O_2 to the tissues.
- In the presence of hypovolaemia the Htc does not reßect blood loss.
- The presence of individual risk factors can mean that the transfusion triggers need to be different from those indicated.

Legend:
RCC: red cell concentrate; GoR: grade of recommendation; TT: transfusion therapy;
*: Hb values below 60 g/L may be tolerated if evaluation of the patient shows that there are no risk factors and that compensatory mechanisms are adequate;
**: the individual patient must be evaluated in order to determine whether transfusion therapy is indicated to raise the Hb above 100 g/L.

blood loss the criteria reported in Table VI can be used. Numerous studies have shown that in such patients there is no signiÞcant difference in mortality at 30 days whether a restrictive transfusion policy or a liberal transfusion policy is used (threshold haemoglobin concentration for ordering transfusion of 70-80 g/dL or about 100 g/dL, respectively). There is evidence that a restrictive transfusion policy does not cause a signiÞcant increase in mortality, cardiac morbidity or duration of hospital stay. One possible exception is the patients with underlying cardiovascular disease (*Grade of Recommendation: 1C+*)[6,91-100].

Transfusion of platelet concentrates and fresh-frozen plasma

The decision to transfuse platelet concentrates must not be based exclusively on the platelet count, but must also take into account the patient's clinical condition (in particular a body temperature above 38.5 °C, plasma coagulation disorders, recent haemorrhages and neurological deÞcits) (*Grade of recommendation: 2C*)[36,38,62,68,83,86,89,90,101-104].

In the post-operative patient with normal platelet function, transfusion of platelet concentrates is rarely indicated if the platelet count is greater than $100x10^9$/L, while it seems necessary if the count is below $50x10^9$/L and there is ongoing excessive bleeding (*Grade of recommendation: 2C*)[36,38,62,68,83,86,89,90,101-104].

In cases of intermediate platelet counts (between $50x10^9$/L and $100x10^9$/L), a transfusion must be considered in specific circumstances, including platelet dysfunction, a high risk of bleeding and a risk

of bleeding into critical sites such as the eyes and brain (*Grade of recommendation: 2C*)[36,38,62,68,83,86,89,90,101-104].

In the case of platelet function defects, whether congenital or acquired (e.g. due to antiplatelet drugs, cardiopulmonary bypass), platelet transfusions are indicated, independently of the platelet count, in the presence of peri-operative bleeding not related to the surgery or other clotting disorders (*Grade of recommendation: 2C*)[36,38,62,68,83,86,89,90,101-104]. In patients with acute disseminated intravascular coagulation (DIC) who have substantial bleeding and thrombocytopenia, platelet transfusion may be indicated to maintain the platelet count around $50x10^9$/L (*Grade of recommendation: 2C*)[105].

In patients with DIC who are not bleeding, prophylactic transfusion of platelet concentrates is reserved to those cases in which the thrombocytopenia and stratiÞcation of bleeding risk suggest a high probability of bleeding (*Grade of recommendation: 2C*)[105].

When the thrombocytopenia is due to increased platelet destruction (heparin-induced thrombocytopenia, autoimmune thrombocytopenia, thrombotic thrombocytopenic purpura) prophylactic platelet transfusion is ineffective and rarely indicated (*Grade of recommendation: 2C*)[36,38,62,68,83,86,89,90,101-103].

In patients who are anaemic and thrombocytopenic (platelet count $\leq 20x10^9$/L), but not actively bleeding, an increase in the Htc to around 30% can reduce the risk of haemorrhage (*Grade of recommendation: 1C+*)[68,102,106-118].

The platelet count should be measured before, 1 hour after and 20-24 hours after the transfusion of the platelet concentrate and the corrected count increment should be calculated (*Grade of recommendation: 1C+*)[68].

Transfusion of FFP is indicated for the correction of congenital deficiencies of clotting factors for which a speciÞc concentrate does not exist, and for multiple acquired deÞciencies of such factors (acute or chronic liver disease), when the prothrombin time (PT) or activated partial thromboplastin time (aPTT), expressed as a ratio, is greater than 1.5, in the presence of bleeding not related to the surgery (or to prevent it, in the case of congenital factor deÞciencies in the absence of the speciÞc concentrates), microvascular bleeding in patients undergoing massive transfusion, acute DIC in the presence of ongoing bleeding, together with correction of the underlying cause (*Grade of recommendation: 1C+*)[36,38,62,66,68,83,86,89,90,105,119-131].

In the case in which the PT and aPTT cannot be obtained in a reasonable time, a transfusion of FFP can be given in any case in an attempt to stop the microvascular bleeding due to the coagulation defect (*Grade of recommendation: 1C+*)[36,38,62,66,68,83,86,89,90,119-131].

The recommended initial dose of FFP is 10-15 mL/kg of body weight. The patient's clinical condition and laboratory parameters should be monitored as these may justify the administration of higher doses (up to 30 mL/kg) of FFP (*Grade of recommendation: 1C+*)[68,105,129].

FFP is not recommended for the correction of congenital or acquired deÞciencies of clotting factors in the absence of bleeding, nor for the correction of deranged haemostasis in patients with acute or chronic liver disease who do not bleed (*Grade of recommendation: 1C+*)[36,38,62,66,68,83,86,89,90,119-131].

Autotransfusion with post-operative salvaged blood

The rationale of post-operative blood salvage

The transfusion of allogeneic RCC is undoubtedly effective, but exposes patients to the risk, albeit limited, of adverse reactions that include infectious diseases and possible immunodepression, with a consequent increase in the possibility of post-operative infections[132-137].

Autotransfusion with post-operatively salvaged blood is, theoretically, a simple and economic method of reducing the use of allogeneic blood; its utility in elective operations, in particular for orthopaedic and heart surgery, has been reported in numerous studies, most of which were, however, conducted in limited numbers of patients.

Absolute contraindications to the use of this procedure are bacterial contamination of the surgical Þeld and haematological disorders that enhance the lysis of red blood cells, such as thalassaemia and sickle cell anaemia (*Grade of recommendation: 1C+*)[138].

Devices for post-operative blood salvage

POBS consists in collecting, into an appropriate container, the blood that a patients loses through surgical drains, and subsequently reinfusing the blood back into the patient. Two systems can be used for

this procedure: "unwashed" and "washed" systems.

In the unwashed system the blood is transfused from the container connected to the drains to the infusion set and is reinfused without undergoing treatment.

The blood is passed through two filters, the Þrst with a mesh of 100-200 μ to retain Þbrin and macroaggregates and a second one with a 40 μ mesh to trap microaggregates. Anticoagulation is not necessary since the blood does not contain Þbrinogen. This system involves simple, economic and easy to use equipment.

In the washed system speciÞc equipment is used to centrifuge the collected blood, eliminate the supernatant, wash the red blood cells and resuspend them in saline solution. This system is more expensive and the staff using it require careful training[139].

Characteristics of blood collected in the post-operative period

Blood collected by POBS is not identical to venous blood in that it is diluted and contains lipid particles, bone fragments, free Hb and a series of bioactive contaminants such as activated clotting factors, Þbrin degradation products, and inßammatory mediators (Table VII); these substances can be responsible for numerous adverse reactions.

Unwashed blood has a Htc between 20-30% and lower levels of Hb, red blood cells, platelets and leucocytes compared to the levels in venous blood. This is a result of haemodilution, Þltration and a certain degree of haemolysis, as demonstrated by the increase in free Hb and cellular debris. It is thought that free Hb may be responsible for renal damage; furthermore, erythrocyte stroma may have a procoagulant action, leading to DIC. The undamaged erythrocytes do not seem to have morphological or functional abnormalities and have normal energy metabolism and viability[139-142].

Following activation of coagulation and fibrinolysis, unwashed blood contains activated clotting factors and Þbrinogen degradation products, whereas it lacks factor V, factor VIII, antithrombin, Þbrinogen, protein C and plasminogen. Reinfusion of this blood can lead to both thrombotic and haemorrhagic changes in coagulation[139,140,142-144].

Unwashed blood also contains large amounts of bioactive contaminants such as cytokines and anaphylatoxins deriving from the degranulation of platelets and leucocytes, and from the activation of complement and the inßammatory cascade. These substances can cause adverse reactions such as fever, tachycardia, hypotension, altered immune status, or severe adverse reactions related to damage to the microcirculation, such as acute respiratory distress syndrome, SIRS, and multiorgan failure [139,140,142,145-150].

Table VII - Characteristics of post-operative salvaged blood.

Haematological and biochemical parameters
RBC↓, Hb↓, Htc↓, free Hb↑, LDH↑, K^+↑
WBC↓, PLT↓
RBC: MCV→, 2,3-DPG→, ATP↑
Bioactive contaminants
Activation of coagulation: FXIIa↑, FXIIIa↑, FV↓, FVIII↓ , AT↓, FG↓↓
Activation of Þbrinolysis: FDP↑, D-dimer↑, tPA↑
Platelet degranulation: serotonin↑, histamine↑, PAI-1↑, TxA_2↑, TxB_2↑↑, PF_4↑
Leucocyte degranulation: IL-1α↑, IL-6↑↑, IL-8↑, TNF-α↑, elastases↑, EPX↑, MPX↑, PGE_2↑, ECP↑, PGI_2↑, leucotrienes↑
Complement activation: C1↓, C3↓, C5↓, C3a↑, C5a↑
Activation of inßammation: free radicals, endothelin, phopholipase A_2, microaggregates

Legend:
2,3-DPG: 2,3-diphosphoglycerate; AT: antithrombin; ATP: adenosine triphosphate; C1, C3, C5: complement components 1, 3 and 5; C3a, C5a: activated complement components 3 and 5; ECP: eosinophil cationic protein; EPX: eosinophil protein X; FDP: Þbrinogen degradation products; FG: Þbrinogen; FV: factor V; FVIII: factor VIII; FXIIa: activated factor XII; FXIIIa: activated factor XIII; Hb: haemoglobin; Htc: haematocrit; IL-1α: interleukin 1α; IL-6: interleukin 6; IL-8: interleukin 8; K+: potassium ions; LDH: lactate dehydrogenase; MCV: mean corpuscular volume; MPX: myeloperoxidase; PAI-1: plasminogen activator inhibitor type 1; PF_4: platelet factor 4; PGE_2: prostaglandin E_2; PGI_2: prostaglandin I_2; PLT: platelets; RBC: red blood cells; TNF-α: tumour necrosis factor α; tPA: tissue plasminogen activator; TxA_2: thromboxane A_2; TxB_2: thromboxane B_2; WBC: white blood cells; ↑: increased; ↓: decreased; →: unchanged.

It has been demonstrated that the above listed contaminants are not only present in unwashed blood collected post-operatively, but are also present in the patient who receives this blood. There have been numerous reports of severe, and sometimes even fatal, complications. The safety of unwashed blood is still subject of discussion, although most of the numerous studies carried out have reported a limited number of severe complications[36,150].

In order to improve the quality of unwashed blood and reduce the risk of potential adverse reactions, the following strategies have been proposed: limiting the period of collecting the blood (for a maximum 6 hours from the end of the operation), limiting the amount of blood reinfused (total volume reinfused: less than 1,000 mL), sedimentation of the product for 20 minutes following its collection and elimination of the supernatant[12,36,90,139,151].

Unwashed blood is, however, a product with a very variable quality, which is generally poor and does not conform with the standards of modern transfusion medicine; its use in the context of POBS programmes is not considered sufficiently safe and effective and does not seem advantageous from an economic point of view (*Grade of recommendation: 1C+*)[36,150].

In the case of the washed system, the blood is centrifuged and 95-99% of the supernatant is removed; the red blood cells are washed and then resuspended in saline. The washed blood is a concentrate of normally functioning, viable red blood cells without bioactive contaminants. This product conforms with transfusion medicine standards, appears to be effective, does not expose the recipient to the risk of adverse reactions and, if used in the presence of substantial loss of blood, can be advanrageous from an economic point of view (*Grade of recommendation: 1C+*)[145,148,152-165].

Efficacy of post-operative blood salvage in orthopaedic and cardiovascular surgery

Since the 1990s numerous studies have been published on POBS in patients undergoing elective orthopaedic or cardiovascular surgery. Most of these studies were retrospective and although there have been a few randomised studies, these usually investigated limited numbers of patients and produced notably heterogeneous results (Tables VIII and IX)[166-206].

The results of the randomised studies were analysed in a Cochrane meta-analysis in 2006 in which it was concluded that the use of POBS reduces the percentage of patients who require transfusion of allogeneic blood and also the amount of allogeneic blood transfused[138]. The efficacy of the procedure is greater in orthopaedic surgery than in heart surgery, with the mean reduction in the risk of exposure to allogeneic blood being 58% and 23%, respectively.

There is little difference between the use of washed and unwashed blood in orthopaedic surgery, whereas unwashed blood seems to be only marginally effective in heart surgery.

The use of POBS does not seem to cause a significant increase in severe post-operative complications (thrombosis, infections, renal failure, myocardial infarction, need for repeat surgery because of bleeding), an increase in the time spent in hospital, or an increase in mortality. The authors did, however, highlight the limitations of the studies examined (small

Table VIII - Characteristics of the randomised, controlled studies: orthopaedic surgery.

Authors	Year	Type of operation	N. of patients enrolled	Type of blood transfused
Lorentz *et al.*[166]	1991	hip	64	washed
Slagis *et al.*[167]	1991	hip/knee	109	washed
Menges *et al.*[168]	1992	hip	42	washed
Koopman *et al.*[169]	1993	hip/spine	60	washed
Mah *et al.*[170]	1995	knee	99	washed
Rollo *et al.*[171]	1995	hip	73	washed
Ekback *et al.*[172]	1995	hip	45	washed
Shenolikar *et al.*[173]	1997	knee	100	washed
Thomas *et al.*[174]	2001	knee	231	washed
Clark *et al.*[175]	2006	hip/knee	398	washed
Majowski *et al.*[176]	1991	knee	40	unwashed
Gannon *et al.*[177]	1991	knee	239	unwashed
Heddle *et al.*[178]	1992	knee	81	unwashed
Mauerhan *et al.*[179]	1993	knee/hip	111	unwashed
Healy *et al.*[180]	1994	hip/knee/ spine	128	unwashed
Riou *et al.*[181]	1994	spine	50	unwashed
Rosencher *et al.*[182]	1994	knee	30	unwashed
Simpson *et al.*[183]	1994	knee/hip	24	unwashed
Ayers *et al.*[184]	1995	hip	232	unwashed
Rollo *et al.*[185]	1995	hip	78	unwashed
Newman *et al.*[186]	1997	knee	70	unwashed
Adalberth *et al.*[187]	1998	knee	90	unwashed

Table IX - Characteristics of the randomised, controlled studies: heart surgery.

Authors	Year	Type of intervention	N. of patients enrolled	Type of blood transfused
Thurer *et al.*[188]	1979	CABG	113	unwashed
Dietrich *et al.*[189]	1989	CABG	100	unwashed
Page *et al.*[190]	1989	CABG and valves	100	unwashed
Eng *et al.*[191]	1990	CABG	40	unwashed
Shirvani[192]	1991	CABG	42	unwashed
Lepore *et al.*[193]	1992	CABG and valves	135	washed
Schonberger[194]	1993	CABG	40	unwashed
Laub *et al.*[195]	1993	CABG	50	unwashed
Ward *et al.*[196]	1993	CABG and valves	35	unwashed
Axford *et al.*[197]	1994	CABG and valves	32	unwashed
Bouboulis *et al.*[198]	1994	CABG	75	unwashed
Fragnito *et al.*[199]	1995	CABG	82	unwashed
Schmidt *et al.*[200]	1996	CABG	120	unwashed
Unsworth-White *et al.*[201]	1996	CABG	105	washed
Zhao *et al.*[202]	1996	CABG and valves	42	unwashed
Dalrymple-Hay *et al.*[203]	1999	CABG and valves	112	washed
Martin *et al.*[204]	2000	CABG and valves	198	unwashed
Naumenko *et al.*[205]	2003	CABG	66	washed
Zhao *et al.*[206]	2003	CABG	60	unwashed

Legend:
CABG: coronary artery bypass grafting

numbers of patients and high heterogeneity of results) and expressed the hope for larger, methodologically rigorous, controlled studies[138].

On the basis of considerations related to efÞcacy, safety and costs, the practice of POBS appears to be justiÞed in major orthopaedic surgery (replacement of hip and knee joints, vertebral column operations) while it does not seem useful in heart surgery or vascular surgery, except in selected cases (for example, in patients who refuse a transfusion or who have complex immunohaematological problems) (*Grade of recommendation: 2C+*)[36,138].

In any case, it is recommended that washed blood is preferred in both orthopaedic surgery and in any other possible Þelds of use (*Grade of recommendation: 1C+*)[145,148,152-165].

Nevertheless, if unwashed blood is used, it is recommended that the concentration of free Hb is assayed before reinfusing the blood, with the aim of determining that the degree of haemolysis is less than 0.8% of the red cell mass contained in the product transfused into the patient (*Grade of recommendation: 1C+*)[63-67].

It is suggested that the following formula is used to calculate the percentage haemolysis of the blood obtained by POBS (*Grade of recommendation: 2C+*)[207-210]:

$$\text{Haemolysis (\%)} = \frac{(100 - \text{Htc}^{\text{POBS}}) \times \text{free Hb}^{\text{POBS}}}{\text{total Hb}^{\text{POBS}}}$$

Legend:
Htc^{POSB}: Htc of the blood obtained by post-operative salvage.
Free Hb^{POSB}: free Hb in the supernatant or the medium used to suspend the red blood cells.
Total Hb^{POSB}: total Hb in the suspension of red blood cells from POSB.

The POBS procedure should, in any case, be reserved to operations which involve the loss of more than 10% of the total blood volume in the post-operative phase (*Grade of recommendation: 1C +*)[36,138].

Finally, it should be emphasised that the efÞcacy of POBS appears to be greater in those patients whose pre-operative Hb concentration is between 120-150 g/L (*Grade of recommendation: 2C+*)[36,138]; the beneÞt seems to be limited in patients with a pre-operative Hb greater than 150 g/L, in whom the probability of transfusion of allogeneic blood is low, and in patients with a pre-operative Hb below 120 g/L, in whom POBS seems to be effective only if used in combination with other measures aimed at preventing or treating post-operative anaemia.

Furthermore, in daily clinical practice, the levels of efÞcacy and safety of POBS are adequate and comparable to those reported in clinical studies only if the staff delegated to performing the procedure are trained continuously (*Grade of recommendation: 2C+*)[36,138,161-165].

Addendum

The process of developing these Recommendations, in conformity with the indications in the methodological manual of the national programme for

guidelines (Istituto Superiore di Sanità, Agenzia per i Servizi Sanitari Regionali. Programma Nazionale per le Linee Guida - Manuale Metodologico. Milano, Italia: Arti GraÞche Passoni srl; 2002. Available at: http://www.snlg-iss.it/cms/Þles/Manuale_PNLG_0.pdf. Last accessed on: 03/25/2010), made use of systematic literature reviews and updates of already existing recommendations on the subject.

The methodology used to determine the grades of recommendation drew on that presented at the 2004 Consensus Conference of the American College of Chest Physicians (Guyatt G, Schünemann HJ, Cook D, et al. Applying the grades of recommendation for antithrombotic and thrombolytic therapy. Chest 2004; **126**: S179-87).

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

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