Recommendations for the transfusion of plasma and platelets

Giancarlo Liumbruno[1], Francesco Bennardello[2], Angela Lattanzio[3], Pierluigi Piccoli[4], Gina Rossetti[5] as Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) Working Party

[1]UU.OO.CC. di Immunoematologia e Medicina Trasfusionale e Patologia Clinica, Ospedale "San Giovanni Calibita" Fatebenefratelli, Roma;[2]Servizio di Immunoematologia e Medicina Trasfusionale, Azienda Ospedaliera "Civile-Maria Paternò Arezzo", Ragusa; [3]Servizio di Immunoematologia e Medicina Trasfusionale, Azienda Ospedaliera di Carbonara di Bari;[4] Servizio di Immunoematologia e Medicina Trasfusionale, Azienda Ospedaliera di Verona;[5] Servizio di Immunoematologia e Medicina Trasfusionale, Azienda Ospedaliera di Trento; Italy

Plasma

Introduction

The main indication for the transfusion of plasma is to correct deficiencies of clotting factors, for which a specific concentrate is not available, in patients with active bleeding. The products available are: fresh-frozen plasma (FFP), plasma that has undergone viral inactivation with solvent/detergent treatment (S/D FFP), with methylene blue (MB FFP) or with psoralens, in particular amotosalen (S59) and light[1]; inactivation technology using riboflavin will soon be available[2].

Fresh-Frozen Plasma

Definition

A blood component prepared from whole blood or collected by apheresis, frozen within time limits and at a temperature such as to preserve the labile clotting factors adequately[3-5].

FFP prepared from units of whole blood and that derived from apheresis are therapeutically equivalent in terms of haemostasis and side effects *(Grade of recommendation: 1A)*[4].

Properties

FFP contains normal levels of the stable clotting factors, albumin and immunoglobulins. It contains at least 70% of the original coagulant factor VIII and at least similar quantities of the other labile clotting factors and natural inhibitors of coagulation[1,3-5].

FFP for clinical use must not contain clinically significant irregular anti-erythrocyte antibodies. In order to increase its safety, FFP can be quarantined for a minimum period of 4 months.

Physiological individual differences in the concentrations of plasma proteins mean that the generic definition of FFP is applied to products that differ notably in quality.

Solvent/detergent-treated plasma

S/D FFP is a pharmaceutical product, obtained from a pool of about 1,000 units of FFP, with the following characteristics[2,6-34]:

- high batch per batch standardisation;
- declared concentration/activity of the biologically active proteins;
- reduced immunological risks related to the presence of antibodies, cells (or their fragments);
- inactivation of the majority of potentially transmissible pathogens;
- selective elimination of units contaminated by hepatitis A virus or parvovirus B19.

Methylene blue-treated plasma

Methylene blue (MB) is a phenothiazine dye with a virucidal effect[2,35-40]. MB FFP is not a pharmaceutical product, but is derived from the use of an inactivation method applied to single units of plasma.

The content of the biologically active proteins of this product cannot be standardised, so the biological variability of the units remains high.

The potential decrease in the residual infective risk is the same as that for S/D FFP.

There is some evidence in the literature that viral inactivation methods cause a decrease in the concentrations of some clotting factors and inhibitors of coagulation[33-40].

Indications

The transfusion of FFP is indicated in the following situations (Table I):

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Table I – Indications for the transfusion of plasma

Clinical condition	GoR
1. Correction of congenital or acquired deficiencies of clotting factors (for which there is not a specific concentrate), when the PT or aPTT ratio is >1.5:	
- Liver disease:	
- *active bleedi*ng	1C+
- *prevention of bleeding in the case of surgery or invasive procedures*	2C
- During treatment with vitamin K antagonists (if prothrombin complex, which is the first choice treatment, is not available):	1C+
- *in the presence of major or intracranial haemorrhage*	
- *in preparation for surgery than cannot be delayed*	
- Acute disseminated intravascular coagulation with active bleeding, in association with correction of the underlying cause	1C+
- Microvascular bleeding during massive transfusions (>1 blood volume), even before the results of PT and aPTT	1C+
- Deficiencies of single clotting factors, in the absence of specific concentrates (e.g. of FV), in the presence of active bleeding or to prevent bleeding during an invasive procedure	1C+
2. Apheretic treatment of thrombotic microangiopathies (thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, HELLP syndrome), as a replacement fluid	1A
3. Reconstitution of whole blood for exchange transfusions	2C
4. Hereditary angioedema in the case that C1-esterase inhibitor is not available	2C+

Legend: GoR: Grade of recommendation; HELLP: haemolytic anaemia elevated liver enzymes and low platelet count

1. Correction of congenital deficiencies of clotting factors, for which there is not a specific concentrate, or acquired deficiencies of multiple clotting factors, when the PT or aPTT, expressed as a ratio, is > 1.5, in the circumstances listed below[1,3,4,41-67]:

A. Ongoing bleeding in patients with liver disease *(Grade of recommendation: 1C+)*[41-51,56-58,67].

B. Prevention of bleeding, in the case of surgery or invasive procedures, in patients with liver disease *(Grade of recommendation: 2C)*[41-51,56-58,67-70].

C. Patients being treated with vitamin K antagonists, in the presence of major haemorrhage or intracranial bleeding or in preparation for surgery that cannot be postponed *(Grade of recommendation: 1C+)*[42-51,56-58,67], if prothrombin complex concentrate, the treatment of first choice, is not available[55,59-65].

D. Patients with acute disseminated intravascular coagulation (DIC) and active bleeding, in association with the correction of the underlying cause *(Grade of recommendation: 1C+)*[41-51,53,54,56-58,67].

E. Correction of microvascular bleeding in patients undergoing massive transfusion. If the PT and aPTT cannot be obtained within a reasonable period, FFP can be transfused in any case in an attempt to stop the bleeding *(Grade of recommendation: 1C+)*[41-51,56-58,66,67].

F. Deficiencies of single clotting factors, in the absence of the specific concentrate (for example, factor V deficiency), in the presence of active bleeding or in order to prevent bleeding, in the case of surgery or invasive procedures *(Grade of recommendation: 1C+)*[41-51,56-58,67].

2. Apheretic treatment of thrombotic microangiopathies (thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, haemolytic anaemia elevated liver enzymes and low platelet count [HELLP] syndrome), as a replacement fluid *(Grade of recommendation: 1A)* [41-52,56-58,67].

3. Reconstitution of whole blood for exchange transfusion *(Grade of recommendation: 2C)*[71,72].

4. Hereditary angioedema due to deficiency of the inactivator of C_1 esterase, in the absence of the specific plasma derivative *(Grade of recommendation: 2C+)*[50].

Indications in neonates

Coagulation times in the neonate, which, on average, are longer than those in the adult, are not necessarily related to the risk of bleeding[71-74]. This is even more the case in premature neonates; thus, abnormal coagulation test results, in the absence of symptoms or haemorrhagic risk, are not an indication for the transfusion of FFP.

FFP is indicated for bleeding caused by vitamin K deficiency and bleeding (or high risk of bleeding) due

to DIC. It is also indicated for the treatment of congenital deficiencies of single clotting factors, when the specific concentrate is not available *(Grade of recommendation: 2C)*[4,71-74].

FFP should preferably be 'safe', in the sense of having undergone viral inactivation or been quarantined.

For further details, refer to the joint recommendations from the Italian Society of Neonatology and SIMTI[72].

Methods of use

FFP must be thawed between 30 °C and 37 °C in a water bath under continuous agitation or with another system able to ensure a controlled temperature. The plasma must be transfused as soon as possible after thawing, but in any case within 24 hours, if stored at 4 ± 2 °C[4,5].

Refer to the product summary sheet for information on the maximum time between the completion of thawing of S/D FFP and starting its transfusion.

FFP must not be refrozen once it has been thawed *(Grade of recommendation: 1C+)*[4].

Dose regimen

The recommended therapeutic dose of FFP is 10-15 mL/kg of body weight[1,4,43,44,47]. The dose of FFP does, however, depend on the clinical situation and laboratory parameters *(Grade of recommendation: 1C+)*[1,4,43,44,47,50], which may justify the administration of higher doses[75-77].

ABO/RhD compatibility

The plasma used must be ABO-compatible with the recipient (Table II) *(Grade of recommendation: 1C+)*[3,4,50].

FFP does not need to be Rh-compatible; anti-D prophylaxis is not necessary in Rh D-negative recipients of Rh D-positive FFP *(Grade of recommendation: 1C+)*[3,4].

Table II - Transfusion therapy with FFP: selection of the ABO phenotype of units to transfuse

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

Inappropriate indications

- Expansion of circulatory volume;
- hypoproteinaemia;
- correction of immune deficiencies;
- for nutritional purposes;
- correction of congenital or acquired deficiencies of clotting factors in the absence of haemorrhage, or correction of disorders of haemostasis in patients with chronic liver disease who are not bleeding *(Grade of recommendation: 1C+)*[4,42-51,56-58,68,69,71-73,77-80].

Contraindications

Absolute contraindications to the use of FFP are documented intolerance to plasma or its components and congenital deficiency of immunoglobulin A (IgA) in the presence of anti-IgA antibodies[4].

Relative contraindications are heart failure and pulmonary oedema.

Monitoring indices for clinical auditing

- The use of transfusion therapy with FFP in the following situations:
  a) expansion of circulatory volume;
  b) hypoproteinaemia;
  c) correction of immune deficiencies;
  d) for nutritional purposes;
  e) correction of congenital or acquired deficiencies of clotting factors in the absence of haemorrhage, or correction of disorders of haemostasis in patients with chronic liver disease who are not bleeding.
- Evaluation of the appropriateness of the dose of FFP.

Adverse reactions to the transfusion of FFP

- Allergic reactions[3,4,42-51,56-58,71-73]:
  a) mild (urticaria): occur in 1% of patients;
  b) severe and anaphylactic: occur with a frequency of less than 1 case per 100,000 transfusions.
- Transfusion-related acute lung injury (TRALI)[81-85]: non-cardiogenic pulmonary oedema developing within 4-6 hours of the transfusion of FFP. This complication can be avoided by using plasma from male donors who have never been transfused and from nulliparous female donors who have never been transfused, or by using S/D FFP.
- Febrile reactions[3,4,42-51,56-58,71-73]: these occur in less than 1% of patients transfused with FFP and in up

to 10% of patients undergoing plasma exchange.

- Citrate toxicity[3,4,42-51,56-58,71-73]: this can occur after the rapid transfusion of large volumes of plasma and is particularly important in neonates and in patients with liver disease.
- Transmission of infections[3,4,42-51,56-58,71-73]: the process of freezing inactivates bacteria; bacterial contamination and growth, with release of endotoxins, before freezing is extremely improbable. There is, however, still the risk, albeit minimal, of transmission of viral infections or infections due to other unknown or untested pathogens.
- Graft-versus-host disease (GvHD)[4]: no cases of FFP-associated GvHD have ever been reported. Freezing causes the lysis of lymphocytes, so irradiation of the plasma is not necessary.
- Circulatory overload[3,4,42-51,56-58,71-73]: this can occur, particularly in patients with renal or cardiorespiratory failure.
- Inhibitors against deficient proteins[86]: these can develop after the transfusion of plasma in patients with severe deficiencies of clotting factors.

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Platelets

Introduction

The transfusion of platelets is indicated for the prophylaxis and treatment of haemorrhage[1] in patients with thrombocytopenia or with primary or secondary functional disorders of platelets.

Available platelet concentrates

A platelet concentrate (PC) can be obtained from a donation of fresh whole blood, which is centrifuged, or from an apheretic donation[1-4].

The platelet content differs according to the type of product (see appendix B):

- PC from a single unit of whole blood [from platelet-rich plasma or the buffy coat]: 0.45 - 0.85 x 10^{11}.
- PC from a buffy coat pool: minimum content 2.5 x 10^{11}.
- PC from apheresis: minimum content 3 x 10^{11}.
- PC from plasmaplateletapheresis or from a multicomponent sample: minimum content 2 x 10^{11}.
- Cryopreserved platelets from apheresis: platelet count greater than 40% of the platelet content before freezing.

Pools of PC from single units of whole blood and apheretic PC contain about the same amount of platelets; comparative studies have shown that they are therapeutically equivalent, in terms of post-transfusion platelet count increment and haemostatic efficacy, if transfused fresh, and that the incidence of side effects associated with the two types of PCs is similar (*Grade of recommendation: 1A*)[4-8].

Compared to PC from apheresis, PC from a pool expose the recipient to a greater number of donors.

Indications for use

The decision to transfuse PCs must not be based exclusively on the platelet count[1]. The absolute indication is severe thrombocytopenia together with clinically relevant bleeding. All the other indications are more or less relative and depend on the clinical condition of the patient.

Human platelet antigen (HPA) and/or human leucocyte antigen (HLA)-compatible platelets can be used in the treatment of immunised patients. It is advised not to use apheretic platelets from relatives of the patients, or other HLA-compatible individuals, who could be haematopoietic stem cell donors.

After a validated procedure of leucodepletion, apheretic PCs are an acceptable alternative to cytomegalovirus (CMV)-negative PCs for the prevention of CMV infection.

Thrombocytopenia due to reduced platelet production

Thrombocytopenia due to reduced production of platelets is a consolidated indication for platelet transfusion, which is a definitely effective therapeutic intervention in this context[3,4,8,9].

Prophylactic use of PCs is possible, and sometimes inevitable, in very severe cases of thrombocytopenia. In these cases the currently recommended transfusion threshold is 10,000 platelets/μL in clinically stable patients[4,8,9-40], that is, in the absence of all the following clinical conditions[4,8,15,17,19-22,26,27,34-36,39,40]:

- fever > 38.5 °C,
- septic syndrome,
- invasive aspergillosis,
- therapy with amphotericin B[13],
- plasma coagulation disorders,
- major headache,
- altered consciousness,
- neurological deficits,
- alterations of vision,
- recent minor bleeds,
- rapid fall in the platelet count,
- white blood cell count > 75,000/μL.

The exceptions are[4,8,15,17,19-22,26,27,35,36]:

- acute leukaemia (AL), excluding promyelocytic leukaemia (French-American-British [FAB] M3):
  a) when the risk of alloimmunisation and/or platelet refractoriness is particularly high: the recommended threshold is 5,000 platelets/μL;
  b) in the presence of clinical instability, the recommended threshold is 20,000 platelets/μL.
- bladder cancer or necrotic tumours, during active and aggressive treatment: the recommended threshold is 20,000 platelets/μL.

Prophylactic indications

See table III.

Prophylaxis for surgery

In the following circumstances (table III):

- major surgery or invasive procedures such as lumbar puncture, epidural anaesthesia, liver biopsy, endoscopy with biopsy, placement of a central venous catheter (CVC): the suggested approach is to bring the platelet count to above 50,000/μL[4,8,10,18,28,29];
- surgical interventions in critical sites, such as

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Table III – Prophylactic indications for the transfusion of platelet concentrates

	Threshold platelets/μL	GoR
AL, except acute promyelocytic leukaemia (FAB M3), in unstable patients[4,10,15,17,19-22,27,35,36]	20,000	1C+
AL, during a clinically stable period, except acute promyelocytic leukaemia (FAB M3) [4,10,15,17,19-22,27,35,36]	10,000	1A
AL, except acute promyelocytic leukaemia (FAB M3), when the risk of alloimmunisation and/or refractoriness is high[4,10,15,17,19-22,27,35,36]	5,000*	1B
Acute promyelocytic leukaemia (FAB M3) [4,10,15,17,19-22,27,35]	See note@	2C
Bone marrow aplasia and myelodysplasias, in unstable patients or during active treatment[8,26]	10,000	2C+
Bone marrow aplasia and myelodysplasias in stable patients[8,26]	See note#	2C+
Allogeneic bone marrow transplantation[4,10,15,17,19-22,27,35]	10,000	2C+
Autologous peripheral blood stem cell transplantation[39]	10,000$	2C+
Bladder cancers or necrotic tumours, during active and aggressive treatment[8,10]	20,000	1C+
Solid tumours, during active treatment[8,10]	10,000	2C+
Ocular surgery or neurosurgery[4,8,10,18,28-31]	100,000	2C
Major surgery, with other risk factors[4,8,10,18,28-,31]	50,000 - 100,000§	2C+
Major surgery, in non-critical sites[4,8,10,18,28-31]	50,000	2C+
Lumbar puncture, epidural anaesthesia, endoscopy with biopsy, placement of a CVC, liver biopsy[4,8,10,18,28-31]	50,000	2C+
Bone marrow biopsy and marrow aspiration[4,8,10,18,28-31]	Threshold not set	2C+

Legend:
GoR: Grade of recommendation
*: This lower threshold can be used when the reference analysis laboratory is able to guarantee acceptable coefficients of variation (intra-test and inter-test) in conditions of extreme thrombocytopenia.
@: Because of the concomitant changes in haemostasis that often complicate AML M3 at diagnosis, once the bleeding disorder has been controlled, the indications for other leukaemias can be taken as the reference.
#: Long-term prophylactic transfusions should be avoided, since these patients are often stable even with platelet counts below 5,000-10,000/mL and there is an unacceptable risk of alloimmunisation.
$: This threshold should only be used in clinically unstable patients.
§ The indication for platelet transfusions in surgical patients with a platelet count between 50,000 and 100,000/mL is based on the overall risk of bleeding, which is related to the type and extent of the operation, the ability to control intraoperative bleeding, the consequences of uncontrolled bleeding and the presence of factors that can affect platelet function (extracorporeal circulation, renal failure, drugs) and/or other comorbid conditions.

ocular surgery and neurosurgery: a transfusion threshold of 100,000 platelets/μL is suggested[4,8,10,18,28,29].

Therapeutic indications (active bleeding)

The need for PCs, in the presence of thrombocytopenia (platelets < 100,000/μL) or functional defects (including iatrogenic ones) of platelets, depends on the nature and the site of the bleeding, on the presence or absence of coagulation disorders, ongoing treatments, as well as the clinical condition of the patient (Table IV).

1. In patients undergoing transplantation of autologous peripheral blood stem cells, provided the patient is clinically stable and PCs are available 24 hours a day, a transfusion strategy aimed at treating World Health Organisation (WHO) grade II or higher haemorrhages can be adopted (Table V), independently of the platelet count (*Grade of recommendation: 2C+*)[39].
2. The surgical patient with active bleeding usually requires platelet transfusion if the platelet count is < 50,000/μL and rarely if the count is > 100,000/μL (*Grade of recommendation: 2C*)[4,8,10,18,28-31].
3. During massive transfusions, when the volume of transfused red cell concentrates is approximately double that of the blood volume, the expected platelet count is 50,000/μL; the suggested transfusion threshold is, therefore, 75,000/μL in those patients with active bleeding in order to guarantee a margin of safety and prevent the platelet count from falling below 50,000/μL, the critical threshold for haemostasis. A higher platelet count has been recommended for patients with multiple trauma caused by high velocity accidents or with lesions involving the central nervous system (*Grade of recommendation: 2C*)[4,41].

Table IV - Therapeutic indications (active bleeding) for the transfusion of platelet concentrates

	Threshold platelets/μL	GoR
Peripheral blood stem cell autologous transplantation, with grade II or higher bleeding according to the WHO bleeding scale.	Threshold not set	2C+
Surgical patient with active bleeding.	50,000 - 100,000	2C
During massive transfusions.	75,000	2C
Extracorporeal circulation with bleeding in the absence of a surgical cause or other coagulopathy.	Threshold not set	1A
Acute disseminated intravascular coagulation with major bleeding and thromboctyopenia.	50,000	2C
Platelet function defects (congenital or acquired) with peri-operative bleeding.	Threshold not set	2C
Autoimmune thrombocytopenia with major and/or dangerous bleeding (e.g. severe intestinal, intracranial or intraocular haemorrhage).	Threshold not set	2C
Post-transfusion purpura with severe haemorrhage while waiting for a response to intravenous immunoglobulins.	Threshold not set	2C

Legend: GoR: Grade of recommendation

Table V - WHO scale for the definition of bleeding severity

Grade 0:

- none.

Grade I (minor bleeding):

- petechiae/ecchymosis;
- epistaxis or oropharyngeal bleeding < 1 hour;
- occult blood in faeces (from trace to 1+);
- haemoglobinuria (from trace to 1+);
- retinal haemorrhage without reduction in vision;
- minimal vaginal bleeding.

Grade II (mild bleeding):

- melaena, haematemesis, haemoptysis, haematuria, haematochezia and abnormal vaginal bleeding that does not require transfusion or increase an already present transfusion need;
- epistaxis or oropharyngeal bleeding > 1 hours;
- occult blood in faeces (moderate or from 2+ upwards);
- haemoglobinuria (moderate or from 2+ upwards).

Grade III (major bleeding):

- melaena, haematemesis, haemoptysis, haematuria, abnormal vaginal bleeding, haematochezia, epistaxis and oropharyngeal bleeding that requires transfusion of one or more units of red cell concentrates/day;
- central nervous system bleeding detected by CAT without clinical consequences;
- bleeding from the site of venipuncture or insertion of a central venous access or catheter that requires transfusion support.

Grade IV (disabling bleeding):

- retinal haemorrhage with reduction of vision;
- central nervous system haemorrhage with neurological signs and symptoms;
- bleeding within vital organs (intrapericardial or pulmonary haemorrhage);
- massive haemorrhage compromising haemodynamics;
- fatal haemorrhage independently of the site.

4. Extracorporeal circulation: it is recommended that platelet transfusions are reserved for patients who, at the end of the operation, have bleeding that is not related to the surgery or other coagulation disorders (*Grade of recommendation: 1C+*)[4,31].
   The platelet count is not indicative in these cases, since these patients have secondary alterations in platelet function, and the decision to transfuse platelets must be guided by clinical criteria (microvascular bleeding and excessive post-operative anaemia) (*Grade of recommendation: 2C*)[4].
5. In acute DIC, in the presence of considerable haemorrhage and thrombocytopenia, in addition to treating the underlying disease and restoring normal levels of clotting factors, the platelet count must be monitored and coagulation screening tests (PT, aPTT, fibrinogen, antithrombin) be performed. There is a lack of consensus on the target platelet count, but in the presence of substantial bleeding, it is reasonable to maintain the count around 50,000/μL (*Grade of recommendation: 2C*)[4,31,42].
6. Disorders of platelet function (congenital or acquired): platelet transfusions are indicated only in the case of perioperative haemorrhage (*Grade of recommendation: 2C*)[4,31].
   Recombinant activated factor VII is indicated for patients with Glanzmann's thrombasthenia who are refractory to platelet transfusions (*Grade of recommendation: 2C*)[4,31].

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Table VI – Indications for the transfusion of platelet concentrates in neonatology

	Threshold platelets/μL	GoR
Alloimmune thrombocytopenia: PC from donors lacking the antigen responsible (if necessary, from the mother, washed, irradiated and suspended in ABO compatible plasma	20,000 - 30,000	2C
Any type of thrombocytopenia	20,000 - 30,000	2C
In the following cases: birth weight < 1,000 g, previous intraventricular/intraparenchymal cerebral haemorrhage (48 - 72 h), concomitant coagulopathy, critically ill neonate (with sepsis or fluctuating arterial blood pressure), during an invasive procedure	30,000 - 50,000	2C
Active bleeding	50,000 - 100,000	2C

Legend: GoR: Grade of recommendation

7. Autoimmune thrombocytopenia: platelet transfusions are only indicated in cases of major and/or dangerous haemorrhage (for example, severe intestinal, intracranial and intraocular haemorrhages) (*Grade of recommendation: 2C*) [4,31,43,44].
8. Post-transfusion purpura: PCs should be used only in an attempt to treat severe haemorrhages in the acute phase and while waiting for a response to intravenous immunoglobulins (*Grade of recommendation: 2C*)[4,31].

Indications in neonates

See table VI.

1. Platelets < 20,000 - 30,000/μL: consider prophylactic transfusion in all cases (*Grade of recommendation: 2C*)[4,12,31,45-52]. In the case of alloimmune neonatal thrombocytopenia select PCs from donors lacking the antigen involved (possibly from the mother, in which case the PC must be washed, irradiated and resuspended in plasma that is ABO-compatible with the neonate).
2. Platelets 30,000 - 50,000/μL: consider prophylactic transfusion in the following cases (*Grade of recommendation: 2C*)[4,31,45-52]:
   - in neonates with a birth weight ≤ 1,000 g in the first week of life;
   - previous intraventricular/intraparenchymal cerebral haemorrhage (48 - 72 h);
   - concomitant coagulation disorder;
   - in the 'critical' neonate (with sepsis or fluctuating arterial blood pressure);
   - during invasive procedures;
3. Platelets 50,000 - 100,000/μL: in neonates who are bleeding (*Grade of recommendation: 2C*)[4,31,45-52].
4. Do not transfuse when the platelet count is > 100,000/μL (*Grade of recommendation: 2C*)[4,31,45-52].

For further details refer to the recommendations issued jointly by the Italian Society of Neonatology and SIMTI[52].

Transfusion practice

- In thrombocytopenic patients, an increase in the haematocrit up to around 30% can reduce the risk of haemorrhage (*Grade of recommendation: 1C+*)[53-63].

Average dose of PC for each transfusion[4,12,31]:

- Paediatric patients: 0.5 x 10^{11} platelets/10 kg (one PC from whole blood every 10 kg)
- Adult patients: about 3 x 10^{11} platelets (one apheretic PC or one PC from a pool of five to eight PCs from whole blood or from a buffy coat pool).

Calculation of the dose of platelets to transfuse

- The dose of platelets to transfuse can be calculated using the following formula:

$$\text{Platelet dose } (\times 10^{11}) = \frac{PI \times BV \times 1.5}{100}$$

PI: target platelet count increment
BV: patient's blood volume (L) (body surface area in m^2 x 2.5, or weight in kg x 0.8)
1.5: correction factor for splenic uptake

Verifying the efficacy of platelet transfusions

- It is essential to monitor the efficacy of platelet transfusions in order to guide the use of subsequent transfusions; the suggested means of doing this is to measure the platelet count before, 1 hour after and 20-24 hours after the transfusion, calculating the so-called corrected count increment (CCI) (*Grade of recommendation: 1C+*)[4,12,31]:

$$CCI = \frac{PC\text{-}POST - PC\text{-}PRE}{N.\ of\ platelets\ transfused\ (x\ 10^{11})} \times BSA$$

CP-POST: platelet count post-transfusion (PLT/μL)
CP-PRE: platelet count pre-transfusion (PLT/μL)
CCI: corrected count increment
BSA: body surface area in m^2

The CCI should be > 7,500 at 1 hour and 4,500 at 20-24 hours.

ABO/RhD compatibility

The PCs transfused must be ABO-identical, or at least ABO-compatible, in order to give a good yield (Table VII)[3,4,10,31].

Group O PC can be used for patients with blood groups A, B, and AB only if they are resuspended in additive/preservative solutions, or if negative for high titre anti-A/A,B [critical titre (in a gel-test) of anti-A/A,B: IgM ³ 1:64 and/or IgG ³ 1:256] (*Grade of recommendation: 2C+*)[64-67].

ABO-incompatible PCs have reduced efficacy and, preferably, should not be used (*Grade of recommendation: 1C+*)[4,10,31,64-67].

Rh-negative patients, in particular women of childbearing age, should receive, if possible, RhD-negative PC (*Grade of recommendation: 1C*)[4,8,10].

In the case of a transfusion of a RhD-positive PC to a RhD-negative women of childbearing age, 250 UI (50 μg) of anti-D immunoglobulin should be administered, a dose able to cover the transfusion of five therapeutic doses of PC in 6 weeks (*Grade of recommendation: 1C*)[4,8,10].

Table VII – Transfusion therapy with PLTs: selection of the ABO phenotype of units to transfuse

ABO phenotype of the recipient	ABO phenotype of units to transfuse (in order of preference)
O	O, A, B, AB
A	A, AB (O after plasma removal and resuspension in additive solutions)*
B	B, AB (O after plasma removal and resuspension in additive solutions)*
AB	AB (A, B, O after plasma removal and resuspension in additive solutions)*

In case single donor platelet concentrates are transfused is desirable to use ABO-compatible platelets and, whenever this is not feasible, it is advisable to assess the level of red cell contamination of single units.
Legend: * = or negative for high titre anti-A/A,B

Refractoriness

A low CCI already in the first hour (< 7,500) is often associated with alloimmunisation to leucocyte and platelet antigens. This type of refractoriness can be caused by antibodies against HLA class I antigens (A and B) or against platelet-specific antigens (in particular HPA-1a)[44].

A normal CCI at 12 hours and a low one (< 4,500) at 20 - 24 hours is usually related to reduced survival of the platelets as a result of non-immunological causes such as[64]: fever, sepsis, splenomegaly, administration of amphotericin B, substantial bleeding, DIC.

Patients with a low CCI on two or more occasions fulfil the criteria for a diagnosis of refractoriness to platelet transfusions. These patients should be investigated to identify immunological or non-immunological causes of the refractoriness. The use of ABO-compatible and fresh PCs (produced within less than 2 days of transfusion) is important in order to determine whether the cause of the refractoriness is antibody-mediated; in fact, platelets collected more than 48 hours before transfusion give a reduced post-transfusion yield and have a shortened survival in patients with clinical conditions that are among the non-immunological causes of refractoriness.

Treatment of refractory patients (*Grade of recommendation: 2C+*)[4,8,31,64,68-72]:

- Transfusion of fresh platelets.
- Wait 2 hours after the infusion of amphotericin B.
- Transfusion of compatible platelets chosen from:
  - HLA-compatible donors;
  - donors compatible according to cross-matching tests.

The transfusion of HLA-compatible platelets, for patients with refractoriness of an immunological origin, should not be considered a first line strategy because it would be necessary to have at least 1,000 donors of typed apheretic platelets.

Recombinant activated factor VII is indicated for patients with Glanzmann's thrombasthenia who are refractory to platelet transfusions (*Grade of recommendation: 2C*)[4,31].

Inappropriate indications

- Thrombotic thrombocytopenic purpura and other microangiopathies[4,12,31,73], such as: haemolytic-uraemic syndrome and HELLP syndrome: the

transfusion of platelets is contraindicated (given that it can be associated with a worsening on the disease), except in the presence of life-threatening haemorrhage.
- Heparin-induced thrombocytopenia, except in episodes of life-threatening bleeding[4,12,31,74].
- Autoimmune thrombocytopenia, except in episodes of life-threatening bleeding[4,12,31,43].
- "Chronic" DIC in the absence of bleeding[4,31,42].
- Prophylaxis during extracorporeal circulation[4,31].
- Prophylaxis during massive transfusion[4,41].
- Post-transfusion purpura.

Monitoring indices for clinical auditing

The use of transfusion therapy with PCs in the following circumstances:
- Prophylaxis at a transfusion threshold higher than recommended.
- "Chronic" DIC in the absence of bleeding.
- Autoimmune thrombocytopenia, except in cases of life-threatening bleeding.

Indications for specifically treated PC

PCs can subjected to particular treatments such as: leucodepletion, cryopreservation, washing and irradiation[1,2,4].

1. **Leucodepleted PC**
   Leucodepletion ensures (*Grade of recommendation: 1C*)[4,75-77]:
   - a reduction in the risk of immunisation against leucocyte antigens (HLA) and prevents refractoriness to platelet transfusions;
   - a reduction in febrile non-haemolytic reactions;
   - a reduction in the risk of rejection in candidates for haematopoietic stem cell transplantation;
   - a reduction in the risk of transmission of viruses hosted in white blood cells, including CMV.

   For the above reasons, consolidated indications for leucodepleted PC are intrauterine transfusions and transfusions in premature babies, neonates and paediatric patients up to 1 year old.
2. **Cryopreserved platelets (from apheresis)**
   Cryopreserved platelets (from apheresis) should only be used if an HLA and/or HPA compatible PC is needed, and a compatible donor is not immediately available (*Grade of recommendation: 2C*)[1].
3. **Washed PC**
   Washed PCs can be prepared for patients who have repeated reactions after transfusion of platelets or for patients with anti-IgA antibodies. Washing also reduces the content of the platelets, which must be resuspended in an additive solution (*Grade of recommendation: 2C*)[1].
4. **Irradiated PC**
   Viable lymphocytes contained in the transfused blood component can cause a severe form of GvHD in severely immunocompromised subjects and in other patients at risk. The lymphocytes in PC can be inactivated prior to transfusion by irradiation[1,2,4,78], at a dose of 25-50 Gy.
   Platelets can be irradiated at any time after their production, without this having any effect on the expiry date of the blood component (*Grade of recommendation: 2C+*)[78].
   The main indications for the use of irradiated PC are reported in the appendix B.

Adverse reactions

- Non-haemolytic transfusion reactions (usually characterised by shivers, fever and urticaria)[1,4]. The incidence of these reactions can be reduced effectively by the use of leucodepleted and/or washed platelets.
- Alloimmunisation to HLA and HPA antigens[1,4]; the risk of anti-HLA immunisation is reduced by the use of leucodepleted platelets; in this case other blood components transfused must also be leucodepleted.
- Post-transfusion infections[1,4]: possible, but very rare, viral diseases, protozoan infections (in particular malaria) and infection by spirochaetes.
- Sepsis[1,4], due to bacterial contamination of the blood; the incidence of this complication is higher than that of the transmission of viral agents, because the platelets are stored at room temperature, which favours bacterial proliferation.
- Post-transfusion purpura[1,4].
- TRALI[1].
- Transmission of other unknown or not tested pathogens.

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Correspondence: Dr. Giancarlo Maria Liumbruno,
Viale Italia, 19
57126 Livorno, Italy
E-mail: giancarlo@liumbruno.it

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Appendix A

Working methods of the study group and grades of recommendation

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

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

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

In detail (Table I):

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

As far as regards the classification by letters:

- **Grade A:** a recommendation derived from the evidence of numerous, consistent randomised studies.
- **Grade C+:** a recommendation derived from the analysis of observational clinical studies, but with very consistent results, or from results unequivocally extrapolated from randomised studies.
- **Grade B:** the clinical studies providing the evidence were randomised, but had important limitations (discordant results, methodological flaws).
- **Grade C:** the recommendation derives from an analysis of observational studies, with less consistent results, or from results extrapolated with a lower degree of certainty from randomised studies; recommendations based on the clinical experience/opinion of experts are also classified as grade C.

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

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

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

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

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

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

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

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

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Table I - Grades of Recommendations

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

Appendix B

Available types of platelet concentrate

1. **Platelet concentrates from single units of whole blood**: these are obtained from fresh whole blood maintained at 22 ± 2 ℃, through centrifugation and subsequent recovery of most of the platelets. At least 75% of samples of the preparations subjected to quality control tests must contain between 0.45 and 0.85 x 10^{11} platelets in 50-60 mL of the suspension medium. Each unit of the platelet preparation must contain < 0.2 x 10^{9} leucocytes if made from platelet-rich plasma or < 0.05 x 10^{9} leucocytes if made from buffy-coat, unless procedures aimed at diminishing the previously mentioned components have been taken. The platelets, if they have been prepared in a closed system, can be conserved at 22 ± 2 ℃ , under continuous agitation, for a variable period depending on the container used but for no more than 5 days after collection. The volume of plasma or preservation fluid must be such as to guarantee a pH between 6.4 and 7.4 throughout the storage period.

2. **Platelet concentrates from a buffy-coat pool**: these are obtained from a pool of five to eight buffy-coats from single units of fresh whole blood and must contain at least 2.5 x 10^{11} platelets. The buffy-coat mixture, compatible with the blood group, must, therefore, be diluted with an appropriate amount of plasma or nutrient solution and centrifuged in order to reduce the number of leucocytes to < 0.05 x 10^{9} in each starting unit. The storage pH and temperature are the same as those for platelet concentrates from whole blood. The duration of the storage period depends on the container used.

3. **Washed platelet concentrates**: these can be prepared for patients with repeated reactions to transfusion of platelets or for patients with anti-IgA antibodies. The washing reduces the protein content, but at the same time decreases the number of platelets. The platelets must be suspended in an additive solution, or in a saline solution, if used immediately.

4. **Platelet concentrates from apheresis**: these are obtained from a single donor who undergoes plateletpheresis. Quality control tests on random samples must show at least 3 x 10^{11} platelets in at least 75% of the samples; platelet concentrates obtained from plasma-plateletpheresis or from a multicomponent collection must contain at least 2 x 10^{11} platelets. If prepared in a closed system, this blood component can be stored at 22 ± 2 ℃ under continuous agitation for a variable period which depends on the container used, but must not be longer than 5 days after the collection. The volume of plasma must be such as to guarantee a pH between 6.4 and 7.4 throughout the storage period.

5. **Platelet concentrates from apheresis suspended in additive solutions**: these are obtained from a single donor who has undergone plateletpheresis or multicomponent collection (plasma-plateletpheresis, erythro-plateletpheresis). The platelets are suspended in a fluid consisting of approximately 30% plasma and 70% additive solution. The platelet content is equivalent to that of the platelet concentrates from apheresis, as are the methods and duration of storage. The volume of preservation fluid must be such as to guarantee a pH between 6.4 and 7.4 throughout the storage period. The lesser amount of plasma present in this type of blood component facilitates allocation of the product, which can be done even without respecting, in adults, donor/recipient ABO group compatibility precisely because of the reduced amount of anti-A/A,B agglutinins. For the same reason, this blood component may be associated with lower risks of

reactions to plasma proteins and TRALI.

6. **Cryopreserved platelets (from apheresis)**: cryopreserved platelets (from apheresis) are prepared by freezing at -80 °C, or at a lower temperature, a platelet concentrate from apheresis collected no more than 24 hours previously. The preparation can be stored in a mechanical freezer at -80 °C for up to 1 year, or in liquid nitrogen vapour at -150 °C for up to 10 years. A cryoprotectant must be used. Before using the platelets, they must be thawed and resuspended in an appropriate solution. After having been thawed, the platelets should be used immediately. In the case of a brief period prior to use, they must be maintained under continuous agitation at 22 ± 2 °C. A reconstituted unit of cryopreserved platelets must have a volume of between 50 and 200 mL, a platelet content greater than 40% of the platelet content prior to freezing, and < 1 x 10^6 leucocytes.

7. **Leucodepleted platelet concentrates**: this blood component is obtained by removing most of the leucocytes from a platelet concentrate.
   - Platelet concentrate from a pool: residual white blood cells < 0.2 x 10^6.
   - Platelet concentrate from apheresis: residual white blood cells < 0.1 x 10^6.

Main indications for irradiation of platelet concentrates

- Intrauterine transfusion and subsequent transfusion in neonates with a birth weight of ≤ 1,500 g and/or gestational age ≤ 30 weeks.
- Congenital cellular immunodeficiency.
- Transfusion with blood components donated by first or second degree relatives (excluding stem cells and lymphocyte concentrates).
- Allogeneic transplant (until the end of GvHD prophylaxis, or a lymphocyte count > 1 x 10^9/L is reached).
- Bone marrow donation for allogeneic transplantation (allogeneic blood components transfused to the donor before and during explantation).
- Bone marrow or peripheral blood stem cell (PBSC) autologous transplantation (in the 7 days before collection of bone marrow or PBSC and up to 3 months after transplantation or 6 months for patients undergoing total body irradiation).
- Hodgkin's lymphoma and patients treated with purine analogues (fludarabine, cladribine and deoxycoformycin).
- The use of irradiated blood components for patients undergoing chemotherapy should be decided on an individual basis, taking into account the intensity of the immunosuppression.
- When none of the above conditions are present, it is not necessary to irradiate blood components transfused to: patients with HIV infection, aplastic anaemia, patients undergoing solid organ transplantation, chemotherapy for non-Hodgkin's lymphoma, acute leukaemias and solid tumours.

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