The Italian Regulatory Guidelines for the implementation of Patient Blood Management

Stefania Vaglio[1,2], Sara Gentili[1], Giuseppe Marano[1], Simonetta Pupella[1], Daniela Rafanelli[3], Gianni Biancofiore[4], Paola Antonioli[5], Claudio Velati[6], Giancarlo M. Liumbruno[1]

[1]Italian National Blood Centre, National Institute of Health, Rome; [2]Department of Clinical and Molecular Medicine, "Sapienza" University of Rome, Rome; [3]Immunohaematology and Transfusion Unit, Pistoia 3 Local Health Authority, Pistoia; [4]Liver Transplant Anaesthesia and Critical Care, University Hospital Pisana, Pisa; [5]Department of Infection Prevention Control and Risk Management, Ferrara University Hospital, Ferrara; [6]Transfusion Medicine and Immunohaematology Department of Bologna Metropolitan Area, Bologna, on behalf of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI), Italy

In 2010, the World Health Organization (WHO) with resolution WHA63.12, urged all Member States to implement Patient Blood Management (PBM)[1]. In Italy, the National Blood Centre, the governmental authority entrusted with the coordination of the blood system, in line with the aforementioned resolution, included the implementation of a PBM programme among the objectives of the 2012 national self-sufficiency plan for blood and blood components[2]. According to the Health Ministry Decree of 4th September 2012, regarding the aforementioned self-sufficiency plan, the concept of PBM was first introduced as a tool to pursue the objective of achieving national self-sufficiency. To reach this goal the Decree established that it was necessary to define and implement innovative and more effective methods and measure to ensure the appropriate clinical and organisational management of blood.

The 2013 programme dealt with the same issue, introducing clearly the wording PBM and underlining the need to promote a multidisciplinary and evidence-based approach aimed at improving the patient's outcome through the three pillars of PBM[3].

In Italy, in 2013 more than 170,000 arthroplasties were performed in 750 facilities with an impact on healthcare expenditure, only for surgical diagnosis-related groups, close to 1.5% of the national healthcare fund[4]. Therefore, in the 2014 national self-sufficiency plan a project, coordinated by the National Blood Centre, foreseeing the first pilot application in the field of elective major orthopaedic replacement surgery was introduced[5]. This project was launched in the orthopaedic units of two large university hospitals in the Regions of Tuscany and Emilia Romagna.

The 2015 national self-sufficiency plan confirmed and took into account a drop in red blood cell transfusion possibly associated with an increased awareness of PBM techniques and strategies that once again were defined as indispensable tools to ensure national self-sufficiency also for that year[6]. Contemporarily, multidisciplinary guidelines on PBM in elective orthopaedic surgery were published[7]. The recommendations were produced by a working group coordinated by the Italian National Blood Centre and involving five scientific societies (the Italian Society of Transfusion Medicine and Immunohaematology [SIMTI]; the Italian Society of Italian Society of Orthopaedics and Traumatology [SIOT]; the Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Therapy [SIAARTI]; the Italian Society for the Study of Haemostasis and Thrombosis [SISET], and the National Association of Hospital Medical Directors [ANMDO])[8]. In the same year, thanks to the endorsement of PBM by the Italian Health Ministry, a very important Decree was issued by the Health Minister regarding provisions related to quality and safety requirements of blood and blood components[9]. Article 25 "Transfusion safety", Paragraph 5 of this Decree[9] states that "*For the prevention of avoidable transfusions and with particular reference to the preparation of the patient who will undergo pre-scheduled surgical treatments, specific programmes are defined and implemented nationwide (Patient Blood Management) on the basis of guidelines to be issued by the National Blood Centre within six months from the entry into force of the present Decree*".

The 2016 self-sufficiency national plan stated that the aforementioned regulatory guidelines had to be based on the scientific recommendations on PBM recently published in the journal *Blood Transfusion*[7]. A set of 32 recommendations with a pragmatic approach to implementing a PBM programme were, therefore, published (Table I). The objectives of this guideline include effective use of pre-operative clinics[10], management of peri-operative anaemia[11-13], detection and treatment of any nutritional deficiencies with haematinics (including intravenous administration of iron when necessary[14,15]), improvement of peri-operative

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Table I - Guidelines for the implementation of Patient Blood Management.

Recommendations for the pre-, intra- and post-operative period	
1	Patients with acquired or congenital coagulopathies and/or thrombocytopathies or positive bleeding anamnesis or those being treated with anticoagulants and/or anti-platelet drugs shall be managed in cooperation with haemostasis and thrombosis specialists.
2	In all adult, clinically stable inpatients who are to undergo a homologous or autologous red blood cell (RBC) transfusion, the adoption of a restrictive transfusion threshold established in cooperation with a transfusion medicine specialist, is recommended. These include critical patients, those with a history of cardiovascular pathologies and those who are to undergo orthopaedic or heart surgery.
3	The threshold for homologous or autologous RBC transfusions in other categories of patients, shall be adopted in cooperation with a transfusion medicine specialist.
4	In clinically stable inpatients needing homologous or autologous RBC transfusions a single unit blood transfusion policy shall be adopted. Further RBC units shall be transfused after a thorough clinical reassessment of the patient.
5	When patients with thrombocytopenia, acquired platelet disorders, or disseminated intravascular coagulation undergo major elective surgery and clinically relevant bleeding or bleeding in vital organs is expected, a prophylactic transfusion of platelet concentrates is suggested. The transfusion threshold, timing and modality shall be established in cooperation with a transfusion medicine specialist.
6	Predeposit autologous blood donation programmes shall be carried out pursuant to the pertinent law in force*. *At the moment, predeposit autologous donation is indicated for: i) patients with rare erythrocyte phenotype or with complex alloimmunisations for whom it is difficult to obtain compatible homologous blood components; ii) donors of bone marrow haematopoietic stem cells; iii) children who are to undergo scoliosis surgery[9].
7	The volume and frequency of blood samples for laboratory tests shall be minimised to prevent iatrogenic anaemia.
Recommendations for the pre-operative period	
8	The preparation of patients who are to undergo non-oncologic major elective surgery, and are expected to have clinically relevant peri-operative bleeding, foresees a careful pre-operative evaluation through clinical and laboratory investigations aimed at providing an exhaustive personal and family anamnesis, detecting anaemia (to minimise homologous RBC transfusion that can lead to a negative outcome), optimising erythropoiesis, identifying and managing bleeding risk as well as assessing and optimising their individual physiological tolerance of anaemia (through the evaluation of cardio-respiratory functional reserve when necessary), and identifying risk factors. The evaluation should be carried out at least 30 days before the planned date of the operation, in order to enable more detailed investigations and/or arrange appropriate treatment.
9	It is recommended that all adult patients who are candidates for elective major surgery for which a multidisciplinary programme of co-ordinated interventions has been established involving the adoption of pharmacological and non-pharmacological techniques aimed at optimising erythropoiesis, minimising blood losses and optimising tolerance of anaemia, before giving consent to one or more of the above-mentioned treatments, receive detailed information on their clinical state and strategies to limit homologous transfusion needs included in the local patient blood management programme; explanatory material prepared ad hoc by the hospital may be used for this purpose.
10	The haemoglobin (Hb) target value before elective major surgery shall be within the normal range according to World Health Organization (WHO) criteria.
11	Anaemia is defined according to Hb threshold values indicated by the WHO.
12	If a state of anaemia is detected, the subsequent laboratory tests shall be performed with the aim of identifying iron or other nutritional deficiencies (folic acid and/or vitamin B_{12}), chronic kidney disease and/or chronic inflammatory disorders.
13	Since the pre-operative Hb value is the main, independent risk factor for an RBC transfusion, any nutritional deficiencies (iron, vitamin B_{12}, folate), once detected, shall be treated with haematinics.
14	In the event of iron deficiency being detected, when the oral administration of iron is ineffective or not tolerated, or when the elective major surgery is scheduled for less than four weeks after anaemia has been diagnosed, the intravenous administration of iron is suggested.
15	Following an appropriate evaluation, to avoid a functional deficiency of iron in patients during treatment with erythropoietic growth factor, it is suggested that intravenous iron be administered.
16	When the administration of intravenous iron is necessary, the utilisation of a single high-dose preparation for the repletion of iron in storage sites is suggested.

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haemostasis[16,17], reduction of blood sample volumes, implementation of restrictive transfusion triggers[18,19] and promotion of a single-unit transfusion policy, to begin with. The active participation of haemostasis and thrombosis as well as blood transfusion specialists is foreseen in the multidisciplinary group that has the task to put into effect the local PBM programme.

Intentionally, no recommendation on the period of time that red blood cells should be stored prior to transfusion was included because we have a decreasing interest in the "new blood - old blood" diatribe and rather agree with the necessity to welcome the opportunity -omics/laboratory studies provided us with to further improve storage quality[20-22].

In January 2017, the Health Ministry sent the guideline to the Italian Regions and invited them to ensure that all health facilities applied it in order to deliver effective healthcare, reduce the need for (homologous) transfusion, improve patients' assistance and reduce costs, including those related to transfusion therapy. Through the Regional Blood Centres, the National Blood Centre will utilise ad-hoc key performance indicators to be developed to monitor the application of the guideline.

Table I - Guidelines for the implementation of Patient Blood Management. *(continued from previous page)*

Recommendations for the intra-operative period	
17	As a pharmacological alternative to improve oxygen transport to correct bleeding-induced hypovolaemia, it is recommended that crystalloid or protein-free colloid solutions be used as first-line therapy, with albumin 5% solution as second-line therapy, when crystalloid or non-protein colloid solutions have already been used at maximum doses, without having produced an adequate clinical response, and when non-protein colloids are contraindicated.
18	With the purpose of containing intra-operative bleeding effectively during elective surgery, it is suggested that combinations of appropriate surgical techniques and instruments to reduce blood loss, minimise trauma to tissues and vessels and promote local haemostasis, which can also be aided by the local administration of vasoconstrictive drugs, be used.
19	With the aim of managing fluid therapy, preference should be given to continuous or semi-continuous haemodynamic monitoring based on the evaluation of flow rather than pressure.
20	It is suggested that intra-operative fluid administration protocols based on haemodynamic optimisation be adopted.
21	In patients who are to undergo surgery where clinically relevant bleeding is expected but who do not have risk factors for hypercoagulability in the preoperative anamnesis, the utilisation of tranexamic acid is suggested.
22	It is recommended that intra-operative blood recovery be used in major surgery in cases in which blood loss is expected to be at least 1,000 mL or in any case ≥20% of the patient's volaemia **despite adopting multimodal strategies**, including the use of pharmacological, surgical and anaesthesiological blood-conservation techniques, and intra-operative cell salvage.
23	It is recommended that point-of-care (POC) instruments be used for the non-invasive continuous measurement of Hb and haematocrit levels.
24	It is suggested that POC instruments be used for the overall monitoring of haemostasis with the purpose of managing clotting factor replacement therapy and limiting the use of transfusion with blood components in elective major heart surgery and all operations with a high risk of bleeding or in the presence of major bleeding.
25	In the presence of massive bleeding during elective major surgery and in association with the correction of the triggering cause, it is suggested that severe hypofibrinogenaemia (<1 g/L) which persists despite treatment with fresh-frozen plasma be treated with fibrinogen concentrate° or, if not available, with cryoprecipitate.
26	In the presence of massive bleeding during elective major surgery and in association with the correction of the triggering cause during massive transfusion, it is suggested that treatment with fibrinogen concentrate°, or if not available with cryoprecipitate, be considered to prevent the fibrinogen level from falling below 1 g/L, the critical threshold for haemostasis.
27	The administration of fibrinogen concentrate°, or if not available cryoprecipitate, is to be preferred to fresh-frozen plasma when there are contraindications to volume overloading.
	° Currently, fibrinogen concentrate is not registered in Italy for this use.
Recommendations for the post-operative period	
28	The utilisation of POC instruments for the non-invasive continuous measurement of Hb and haematocrit levels is suggested.
29	When the administration of iron is necessary, an intravenous therapy is recommended, and where possible through the utilisation of a single high-dose preparation for the repletion of iron in storage sites.
30	Post-operative blood salvage is recommended only in cases where the post-operative blood loss is expected to be ≥10% of the patient's volaemia despite implementing multimodal strategies, including the integrated use of other pharmacological, surgical and anaesthesiological blood-conservation techniques.
31	When post-operative cell salvage is utilised, the use of blood-washing systems is to be preferred.
32	When using non-washing systems, it is suggested that the concentration of free Hb be determined before re-infusing the blood to ensure that the level of haemolysis is less than 0.8% of the red cell mass contained in the product transfused.

Disclosure of conflicts of interest

GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result. The other Authors declare no conflicts of interest.

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Correspondence: Giancarlo M. Liumbruno
Italian National Blood Centre
Via Giano della Bella 27
00162 Rome, Italy
e-mail: giancarlo.liumbruno@iss.it