Transfusion strategies in thalassemia and sickle cell disease SITE-SIMTI-SIdEM Good Practice

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This document is the tool through which the knowledge developed by biomedical research is transferred to daily clinical practice. It does not offer standards of care to which one can refer in acritical and decontextualized manner: these standards must be able to be expressed, for each individual case, on the basis of available clinical information, preferences of the patients and other contextual situations, accurately examined in light of the expertise of healthcare professionals. It is therefore up to the expertise and judgement of the professionals, who carefully listen to particular requests and consider the values expressed by patients, to establish which procedures or treatments are more appropriate to manage individual clinical cases.

The Good Practice (GP) is organized in two large sections:

- a main section which, for each topic of interest, reports a short specific introduction and continues with recommendations for clinical practice in order to allow the reader to access the interpretation of the evidence and the recommendations made by the Authors.
- No. 4 Enclosures where the following is reported:
  1. Enclosure 1 - transfusion yield;
  2. Enclosure 2 - perioperative management and prevention of postoperative complications;
  3. Enclosure 3 - donation of blood, hematopoietic stem cells (HSCs), organs and tissues;
  4. Enclosure 4 - table of matching levels.

Keywords: *hemoglobinopathies, blood transfusion, sickle cell disease, thalassemia, guideline.*

INTRODUCTION

At the beginning of 2024 Italian Society of Thalassemia and Hemoglobinopathies (*Società Italiana Talassemie ed Emoglobinopatie* [SITE]), Italian Society of Transfusion Medicine and Immunohematology (*Società Italiana di Medicina Trasfusionale ed Immunoematologia* [SIMTI]), and Italian Society of Hemapheresis and Cellular Manipulation (*Società Italiana di Emaferesi e Manipolazione Cellulare* [SidEM]) undertook a project aimed at updating and integrating, with a systematic method, the recommendation for transfusion strategies in hemoglobinopathies[1].

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METHODS

To achieve this goal, a systematic review of the available literature starting from 2014 was conducted, followed by the formulation and structured discussion of specific recommendations for clinical practice in hemoglobinopathies.

The panel of experts that developed the previous version has been reconstituted, replacing the members who were no longer available. The experts were flanked by other experts with methodological and organizational skills, in order to create recommendations based on the integration of available scientific evidence together with expert opinion, with the aim of supporting clinicians in the decision-making process, thus improving the appropriateness of care.

The present edition follows a systematic approach borrowed from the approach of the Methodological manual for the production of clinical practice guidelines, edited by the National Center for Clinical Excellence, Quality and Safety of Care. This approach allowed the panel to use already existing guidelines and to contextualize them to the target population, producing recommendations specifically made for hemoglobinopathies.

The identification, evaluation and selection of the available evidence-based guidelines published between January 1st, 2014 and July 31st, 2024, the date of the most recent reference used, was carried out.

The critical evaluation of the guidelines in terms of quality, up-to-dateness and debated topics was assessed by the panel that deemed it necessary to integrate what had been selected with clinical studies focused on specific evidence for hemoglobinopathies.

The search was carried out through a systematic review of the main data sources: specific databases of guidelines (international health agencies producing guidelines; bibliographic databases with reference only to guidelines) and generalist databases. The research was completed manually and asking the panel experts about any "missing papers". The bibliographic search identified a total of 150 titles and abstracts. After a first evaluation, carried out based on abstracts, and a second one, based on full texts, 111 Guidelines and reference documents were considered relevant.

Once the evaluation of the literature review was completed, the Authors proceeded to update the previous document.

The Authors discussed what had been prepared during several plenary meetings held in virtual mode.

Grading scheme

The grading used in this good practice is reported below:

- grade **1A**: strong recommendation based on strong evidence certainties and meta-analyses;
- grade **1B**: strong recommendation based on strong evidence certainties;
- grade **1C**: strong recommendation based on weak evidence certainties;
- grade **2A**: strong recommendation based on moderate evidence certainties;
- grade **2B**: strong recommendation based on moderate-weak evidence certainties;
- grade **2C**: strong recommendation based on weak evidence certainties;
- grade **3A**: conditional recommendation based on strong evidence certainties;
- grade **3B**: conditional recommendation based on moderate evidence certainties;
- grade **3C**: conditional recommendation based on weak evidence certainties;
- grade **4**: conditional recommendation based on expert indication.

Moreover, the answers by the Authors were also formulated based on common clinical experience, even in the absence of evidence or of sufficient supporting evidence, on issues deemed relevant to clinical practice.

The recommmendations were written in a clear and unambiguous language. Where necessary, notes were added including information on limitations and conditions of applicability, as well as details on target populations, interventions, setting and outcomes.

In order to improve wording, solve ambiguities, remove futile or potentially dangerous statements and suggest comments and criticalities, a wording process was performed.The final version of the document was forwarded for an external review, in order to receive comments and proposals for modification or supplementation. The comments received by revisers have been considered by the Authors, who replied to the comments and decided which changes had to be made to the text based on such comments.

It is planned to update the Good Practice every three years, starting from the date of publication. The methodology

followed in the update will be the same used in the present version, or anyway similar to this; literature search will be started from the date on which the present search was carried out.

Once the GP is deemed suitable for publication, it will be published on the SITE and SIMTI websites; it will also be presented at the main conferences on hemoglobinopathies and will be translated and submitted for publication to an international peer-reviewed journal.

GOALS AND MANAGEMENT OF TRANSFUSION THERAPY

Every request for blood transfusion must be preceded by a careful evaluation of the risk-benefit ratio and by awareness of the risk intrinsic to each transfusion act.

The healthcare personnel planning the patient's transfusion therapy must be guaranteed access to anamnestic information relevant to transfusion therapy such as immunizations and adverse reactions.

Transfusion therapy must follow protocols recognized by the scientific community and guarantee high quality standards not conditioned by situations that delay its application.

Transfusion-dependent thalassemia (TDT), transfusion dependent thalassemia major and thalassemia intermedia

Objective: ensuring a normal development and growth by correcting anemia, suppressing ineffective erytrhopoiesis, reducing iron absorption and preventing related complications[2-8].

In patients with TDT, red blood cell transfusion is a mandatory therapeutic choice. The transfusion regimen requires regular frequency, in the most severe forms (thalassemia major), throughout the patient's life starting from early childhood. Regular transfusion therapy associated with iron chelation, which also has oral drugs available, has changed the prognosis of this pathology from unfavourable in the first decade of life to a pathology with an "open prognosis"[4,5].

The transfusion regimen aims at maintaining a pretransfusion hemoglobin value >9,5 g/dL[2,4] in order to ensure a balance between inhibition of marrow erythropoiesis and iron overload from transfusion therapy[9,10] (Grade of recommendation: **2C**).

Pretransfusion hemoglobin (Hgb) levels were chosen based on evidence in a population of TDT patients (No.=779) over a 10-year observation period and on their positive impact on mortality[11].

Higher pretransfusion hemoglobins (e.g., greater than 10) may be chosen in patients with heart disease or with persistent high erythropoietic activity[2,12], e.g., *foci* of extramedullary erythropoiesis.

The volume of red blood cell concentrate to be transfused should preferably be between 10 and 15 mL/kg at a rate of 150-300 mL/h, or rather to be administered over a period of no more than 3 hours. In patients with significantly reduced left ventricular ejection fraction it is advisable not to exceed the volume of 5 mL/kg per session[9,13-15]. The best transfusion strategy involves maintaining the target with the least possible number of hospital admissions.

Non-transfusion dependent thalassemia (NTDT)

Objective: improved tissue oxygenation, suppression of ineffective erythropoiesis and foci of extramedullary erythropoiesis[8].

In NTDT patients transfusion represents a procedure to be used occasionally, at particular moments of the disease (surgical interventions, acute or chronic complications, infectious processes, pregnancy, etc.) or on clinical indications even independent of Hgb values and aimed at preventing complications such as pulmonary hypertension, heart disease, foci of extramedullary erythropoiesis, malleolar ulcers, fatigue or consequent to them[7,16] and reduction of thrombotic risk, especially high in splenectomized patients[7] (Grade of recommendation: **3B**).

Not infrequently NTDT patients become TDT-Transfusion dependent, due to a phenomenon of "phenoconversion"[17], and the recommended transfusion regimen is similar to that indicated for TDT, as is the choice of the blood component to be assigned (**Figure 1**)[18].

Sickle cell disease (SCD)[19]

Objective: in the presence of acute vaso-occlusive crises, interrupt the intravascular sickling process[19-22] by diluting (if a simple transfusion is performed)[23-25], or replacing (if an erythroexchange is performed)[22-27] the circulating pathological red blood cells containing hemoglobin S (HbS) with normal red blood cells containing hemoglobin A (HbA); preventing/reducing hemolytic complications[24], increasing oxygen supply[20,22,24,26] and preventing iron accumulation in case of exchange[8,20,23].

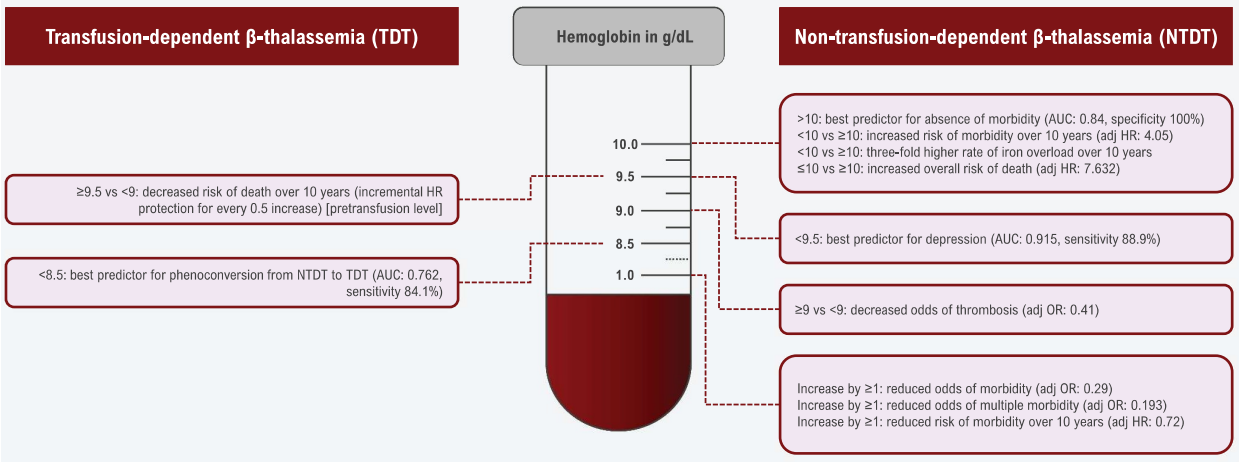

Figure 1 - Association between hemoglobin levels, morbidity and mortality in β-thalassemia[18]

SCDs are characterized by severe clinical pictures that manifest themselves both acutely in a "time dependent" manner with unpredictable and dramatically evolving modalities[18] and chronically. It is important to never underestimate the symptomatology and to guarantee short times for evaluation and early treatment. In the acute setting, transfusion therapy is to be considered a "lifesaving" intervention.

The transfusion regimen can be occasional or periodic:

- ***occasional:*** it is performed in the presence of acute disease complications (e.g., vaso-occlusive crises, acute anemization due to sequestration, intrahepatic cholestasis, infectious processes) or in particular moments such as pregnancy or surgical interventions.
- ***periodic:*** on clinical indications also independent of Hgb values and aimed at the prevention and treatment of chronic complications such as symptomatic anemia, primary and secondary prevention of stroke, pulmonary hypertension, heart disease, foci of extramedullary erythropoiesis, hepatopathy, malleolar ulcers, fatigue or related clinical pictures[8,20,23,28-30].

The key points of the management of SCD are: i) good knowledge of the physio-pathological mechanisms, leading to the choice of the most appropriate therapeutic strategies, at the same time curative and preventive, ii) treatment of organ pathology, and iii) adoption of the simplest and most effective therapeutic modalities[22,31]. The basic therapy for this pathology is represented by hydroxyurea both in pediatric age and in the adults[32-35].

Transfusion therapy can be applied either as a simple transfusion or as an erythroexchange.

Simple transfusion

Simple transfusion is indicated in case of symptomatic anemia and anyway in case of patient's Hgb levels <7 g/dL, (Grade of recommendation: **2C**), but must not be applied when the patient's Hgb >11 g/dL[14,19,25,36].

In pediatric age, simple transfusion in chronic regimen is indicated for the prevention of stroke if transcranial ultrasonography is positive[37,38].

Erythroexchange

Erythroexchange is recommended (Grade of recommendation: **3B**) in cases where it is necessary to rapidly reduce the concentration of HbS without increasing hematocrit and blood viscosity[20,23-25,39], it is also effective in the treatment of chronic complications[19,20,23,24,27] and is advantageous in the prevention of iron overload related to simple transfusions[20,35,36].

At the end of the erythroexchange, the patient's Hgb value must remain <10-11 g/dL: higher values are in contrast with the need to reduce blood viscosity, with a possible worsening of the clinical picture or a negative evolution[19,24,27,36].

For hemoglobin values lower than 9 g/dL, transfusion is indicated before carrying out the exchange procedure.

Erythroexchange can be performed manually or with a cell separator.

Manual erythroexchange

Manual erythroexchange is to be considered a rapidly applicable procedure in the acute phase that can be

performed in any facility, because it does not require instrumentation and qualified personnel but only trained personnel[23,27,36,40] and needs only one vascular access[41]. The Guidelines of the British Society of Hematology and Transfusion[42] recommend that in emergency departments of hospitals where SCD patients are admitted, the staff be trained to perform manual erythroexchange (EEX).

For the calculation of the volumes to be exchanged through manual erythroexchange, the "MEEXCalc" App is available which takes the algorithm reported by Gianesin *et al.* as a reference[40]. The App can be downloaded free of charge from the Android and IOS stores.

Manual erythroexchange in the acute phase, besides resulting in an effective, rapid and timely reduction of the HbS concentration, allows the effective and early removal of plasma containing acute phase proteins[22,23,40,43] such as cytokines, cellular debris, plasma activation proteins.

Erythroexchange with cell separator

Erythroexchange with cell separator (erythrocytapheresis) requires a transfusion facility with personnel who are expert in apheresis procedures. The use of a cell separator also requires the availability of well-functioning peripheral vascular access sites or of a central vascular access, and this can be a problem, especially in pediatric patients[23,24,27,36].

Objectives of erythroexchange

- Maintain Hbs concentration <30-40% because the risk of these patients developing vaso-occlusive crises when HbS is less than 30-40% is significantly reduced[19,20,22-24,26,44];
- HbS concentration <15% if the patient's clinical picture does not improve upon reaching the target of HbS <30% continuing with the erythroexchange program[22];
- The patient's hematocrit (Ht) around 30% because higher values entail an increase in blood viscosity that can be co unterproductive[19,22-24,26,44].

In the exchanges performed in acute conditions, in cases where, despite reaching the target of HbS <30%, there is no improvement in the patient's clinical picture, erythroexchange associated with plasma exchange is indicated to remove circulating cytokines and cell degradation products[22,23,43]. In this case, the exchange fluid can be 4% albumin solution or frozen fresh plasma or a combination of the two, considering that plasma offers the secondary advantage of increasing, albeit transiently, the levels of haptoglobin and hemopexin, which in patients with acute SCD are depleted[22,23,43].

Indications for transfusion therapy in SCD

Indications for transfusion therapy in acute events:

- acute exacerbations of anemia[19,24,36];
- VOC and painful crisis not responsive to standard medical treatment[19,21,22,24,35,36];
- acute chest syndrome[19,24,26,35,36,39,45-47];
- acute neurologic deficit (stroke)[19,20,24,32,35-37,39,46];
- intrahepatic cholestasis[36,48,49];
- multiorgan failure[19,22,24,36,46];
- splenic or hepatic sequestration[24];
- renal infarction;
- priapism.

Acute events of SCD have a time-dependent evolution as the clinical picture can rapidly evolve into a catastrophic and fatal event. Symptoms must never be underestimated and short times must be guaranteed for both evaluation and treatment, as is the case with other time-dependent clinical conditions (e.g., myocardial infarction, stroke, etc.)[35,41]. When a patient with a sickle cell crisis enters the Emergency Room (ER), the transfusion facility in charge must be immediately alerted during the triage evaluation[35,41].

Indications for long-term regular transfusion therapy:

- symptomatic anemia[19,36];
- recurrent acute chest syndrome, not responsive to hydro xyurea[19,24,26,35,39,45,46];
- stroke, primary and secondary prevention[19,20,22,24,32,35,37,39,46,50];
- multiorgan failure in evolution[19,22,24];
- pulmonary hypertension[19,24,32];
- heart disease[19,24,32];
- renal complications[19,24,32,51];
- hepatopathy[52].

Other indications for transfusion therapy:

- recurring splenic sequestration[19,24];
- pregnancy[19,24,36,53];
- preoperative management[19,36,46];
- retinopathy.

Controversial indications for chronic transfusion therapy:

- priapism[54];
- skin ulcers[22,24];
- aseptic necrosis of the femoral head.

Management of the main clinical pictures in sickle cell disease

Please refer to SITE and AIEOP Good Practice for the management of adult and pediatric patients with SCD[55,56].

PREGNANCY

This section only contains indications concerning the identification of the best transfusion product for pregnant TDT/NTDT or sickle cell patients, also considering the transfusion regimen prior to pregnancy.

In particular, an extended phenotyping should be performed with serological or molecular method (ABO, Rh, Kell, Duffy, MNSs, Kidd antigen systems), execution of an Indirect Coombs Test and, if positive, identification and titration of alloantibodies, and subsequent assignment of red blood cell units negative for the antigen towards which the antibody has developed (Grade of recommendation: **2A**).

It is pointed out that women with sickle cell disease who continue or start automated erythroexchange should be checked, by means of targeted ultrasound control, for the absence of potential bleeding sites (e.g., placental abruption). If their presence is documented, it is recommended to use manual erythroexchange.

For the clinical management of pregnant TDT/NTDT or sickle cell women, please refer to SITE Good Practice[53].

CHARACTERISTICS OF BLOOD COMPONENTS

The indications below are applicable for TDT, NTDT, SCD. For each of these pathologies, in an appropriate transfusion regimen, the selection of the erythrocyte concentrate to be assigned to the patient must take into account the characteristics and product specifications described below, see also Enclosure 1[10,24,57-59].

The recommendations for the choice of the erythrocyte concentrate, leukodepleted and resuspended in additive solution, are summarized in (Grade of recommendation: **3B**):

1. Use leukodepleted erythrocyte concentrate obtained by one of the following production methods:
   - apheresis erythrocyte concentrate;
   - erythrocyte concentrate obtained by in-line pre-storage filtration of whole blood, subsequent centrifugation and removal of plasma;
   - erythrocyte concentrate obtained by in-line filtration (pre-storage).
2. Use an erythrocyte concentrate sampled no more than 14 days earlier. In cases of acute anemia, in particular for sickle cell disease, use erythrocyte concentrates sampled no more than 7 days earlier, if possible;
3. Maintain the integrity of the erythrocyte concentrate unit, without carrying out processings aimed at hemoglobin concentration;
4. Maintain the integrity of the erythrocyte concentrate unit, without washing the red blood cells, unless one of the cases described below, in point c), applies;
5. Do not use irradiated units, unless the patient has specific indications for transfusion of irradiated blood components (e.g., cell therapy, etc.).

The ideal blood component for transfusion support of the transfusion-dependent patient with chronic anemia must have the characteristics indicated in[57,60]:

a) the lowest leukocyte content to minimize febrile non-hemolytic transfusion reactions and alloimmunization to leukocyte antigens;
b) the lowest cytokine content to minimize the risks of non-hemolytic transfusion reactions. In line pre-storage filtration of whole blood or of erythrocyte concentrates removes leukocytes from the unit early and minimizes cell degranulation and cytokine release;
c) the minimum time interval from the blood sampling and in any case not exceeding 14 days, subject to the availability of erythrocyte concentrates of the most appropriate phenotype, to optimize the transfusion yield and the oxygen release to the recipient's tissues. In case of transfusion support due to acute anemia, the units assigned should have a sampling date possibly <7 days; if, due to immunological matching reasons, the units to be assigned are >21 days old, if the recipient shows signs of renal failure, washing the units to remove extracellular potassium prevents the risk of hyperkalemia;
d) the lowest plasma concentration/unit (<0,5 g of proteins/unit). This requirement is critical for a limited category of patients (10-15% of patients), in the presence of one of the following problems:
   - IgA deficiency;
   - non-antihistamine-sensitive recurrent allergic reactions;
   - recurrent febrile post-transfusion reactions, also present with the use of leukodepleted red blood cells.

Patients with renal failure who receive erythrocytes with a sampling date >21 days assigned to them to comply with

the immunological match. In these cases, the removal of the donor's plasma, even if present in the erythrocyte concentrate in a very limited quantity (equal to a few tens of mL), is aimed at eliminating extracellular K+ and can be guaranteed by washing the units. Unit washing with automated and closed-circuit mode is recommended.

The choice of the methods to produce erythrocyte concentrates is linked to the organizational aspects of the reference transfusion facility, these characteristics are guaranteed by the following blood products[9,10,57,61].

Leukodepleted erythrocyte concentrate by apheresis

Definition: red blood cells obtained from a donor through a sampling carried out using an automatic cell separator.

Leukodepleted erythrocyte concentrate resuspended in additive solution

Definition: a blood component obtained from whole blood which has undergone decomposition by centrifugation, with removal of plasma and resuspension of the erythrocyte concentrate in additive solution. Leukodepletion is obtained by in-line filtration of whole blood before centrifugation, or by in-line filtration of the pre-storage erythrocyte concentrate.

BLOOD COMPONENT ASSIGNMENT

Patients with continuous transfusion requirements are particularly exposed to the risk of immunological complications of transfusions, in particular the risk of alloimmunization, due to the exposure of the recipient to donor's erythrocyte antigens, which might be foreign to them[10,24,25,46,62,63]. Depending on the degree of immunocompetence of the patient and on the immunogenicity of the erythrocyte antigens, the risk of alloimmunization changes[24,30,46,62].

It has been estimated that in immunocompetent, unselected recipients alloimmunization occurs with a risk ranging from 1 to 1.6%, (in other records 0.3-5%)[24] for each unit of red blood cells transfused, as long as RhD negative recipients have received RhD negative red blood cell units[24]. In patients who have developed irregular alloantibodies it is *always* important to transfuse red blood cells that are free of the antigen against which the alloantibody is directed[24,25,46,64-66], even after a certain period, when the antibody is no longer detectable (anamnestic antibody).

Transfusion dependent thalassemia (TDT)

TDT patients sometimes develop a sort of immunological tolerance, leading to a low incidence of alloimmunization. The specificity of the alloantibodies that develop, however, is almost always linked to differences in the Rh and Kell system between donor and recipient[24,67].

For this reason, it is recommended (Grade of recommendation: **1C**) to select the units of erythrocyte concentrate to be transfused respecting the match for ABO, Rh, K antigen systems (level 2 match)[24].

Non-transfusion dependent thalassemia (NTDT)

NTDT patients are transfused irregularly, often splenectomized and show a higher susceptibility to develop alloantibodies as compared to TDT patients[7]. Also for these individuals the specificity of the alloantibodies that develop is mostly linked to differences in the Rh and Kell system between donor and recipient[24,67].

For this reason, it is recommended (Grade of recommendation: **1C**) to select the units of erythrocyte concentrate to be transfused respecting the match for ABO, Rh, K antigen systems (level 2 match)[24,59].

The classification of blood group matching levels between patient and transfusion units is detailed in Enclosure 5.

Finally, where possible, it is also recommended to match the most immunizing antigens of the minor antigen systems [Duffy, Kidd, MNSs - (level 3 match)][63,66] in patients who begin transfusion therapy in late adolescence to youth-adulthood and are already carriers of at least 1 alloantibody[62,66-68].

Sickle cell disease

In patients with sickle cell disease requiring transfusion therapy, the incidence of alloimmunization is high, with a range of 18-46%[24,36,37,46,64,65]. The difference as compared to TDT patients in chronic transfusion therapy is most likely related to several elements, such as: ethnic differences between donors and recipients, generally irregular and discontinuous transfusion regimen, rarely starting in early childhood[36], chronic inflammatory state that flares up during acute events (e.g., VOC)[24,66], functional asplenia or splenectomy[24,36,66,68,69].

The specificity of the alloantibodies that develop, almost always linked to differences in the Rh and Kell system between donor and recipient[23-25,36,64,65,67], can affect other blood group systems[24,25,36,67,68].

Furthermore, alloimmunization often manifests itself with the presence of mixtures of alloantibodies, which

make it more difficult to find compatible units[24,25,67] and may be accompanied by the presence of autoantibodies[66,67]. For this reason, it is recommended (Grade of recommendation: **1C**) to select the units of erythrocyte concentrate to be transfused respecting at least the match for ABO, Rh, K antigen systems (level 2 match)[24,25,36,46,64,66]: it is proven that this strategy reduces the risk of alloimmunization by 50%[24,25,46].

Extended erythrocyte antigen profile including typing for C/c, E/e, K/k, Fya/Fyb, Jka/Jkb, M/N, and S/s, should be defined for all sickle cell patients (as soon as possible and before transfusion). Direct Coombs Test should also be evaluated.

In non-Caucasic sickle cell patients it is recommended to perform genotypic characterization, which is more specific regarding the identification of antigenic variations affecting the RHD gene and the expression of C and Duffy antigens (Grade of recommendation: **1B**).

Since serological characterization may not be accurate if the patient was transfused in the 3 previous months, it is therefore important to gather information on the antibody status from the facilities where he/she has been previously transfused. Most antibodies are no longer detectable 6-12 months after initial identification[23].

For the transfusion therapy of these patients, erythrocyte concentrates obtained from NON-HbS carrier donors must be used[64,67,68]. In alloimmunized sickle cell subjects, in whom transfusion is anyway considered essential, it is strongly advised to assign erythrocyte concentrates that respect the antigenic pattern of the recipient as much as possible, for the greatest number of antigenic systems[70] (Grade of recommendation: **4**).

In case of late hyperemolitic syndrome[24,46,70-74], please refer to paragraph "Delayed hyperhemolysis syndrome".

PRE-TRANSFUSION TESTS

For patients undergoing continuous transfusion regimens, it is recommended that the assignment of erythrocyte concentration units always occurs using the following pre-transfusion tests[10,24]:

- verification of the ABO-D blood group of the recipient before each transfusion, according to the regulations;
- best match grade (at least for ABO-D, Rh, Kell);
- cross-match for each transfused unit;
- search for irregular antibodies before each transfusion session.

In case irregular antibodies are detected[23,24,46,57,62,64,66,70]:

- verification of the absence of the corresponding antigen on each transfused unit;
- best match grade (also for minor antigenic systems);
- information regarding the appearance of the irregular antibody reported on all medical documentation, so that it is available and consultable at any time, making it usable also by other centers that may take care of the patient occasionally.

In case of documentation of irregular antibodies in a patient coming from another place[23,24,62,64,66]:

- verify the presence of the reported antibody, keeping in mind that it could be an anamnestic antibody (phenomenon of antibody evanescence), the titer of which tends to progressively decrease in the following 5 years, and could therefore be no longer documentable;
- report the current status of antibody detectability in the patient's medical documentation;
- ***always*** check for the absence of the corresponding antigen in the transfused units, even if the presence of the antibody is only anamnestic.

MANAGEMENT AND PREVENTION OF ADVERSE REACTIONS

Adverse reactions

Transfusion therapy with erythrocyte concentrates can cause a series of unwanted and unfavourable effects or adverse reactions[24,25,66] that are classified according to the pathogenetic mechanism and the onset time interval in regard to the transfusion event itself[15,25,44,75,76], as indicated in the following.

Immediate reactions immunological

- Acute hemolytic reaction;
- febrile non-hemolytic reactions;
- allergic reactions (hives, anaphylaxis);
- non-cardiogenic acute pulmonary edema;
- TRALI (transfusion-related acute lung injury).

Immediate reactions non immunological

- Bacterial contamination/septic shock;
- cardiogenic pulmonary edema;
- non-immunological hemolysis;
- electrolyte imbalances (hyperkaliemia, hypocalcemia);
- hemocoagulative modifications and DICd acute lung injury.

Delayed reactions immunological

• Delayed hemolytic reaction.

Delayed reactions non immunological

• Bacterial contamination;
• transmission of viral, bacterial or protozoan diseases;
• cardiogenic pulmonary edema;
• iron overload.

It is advisable to avoid the simultaneous administration of drugs and transfusion therapy to limit the concurrence of possible adverse reactions due to different administrations.

Management of immediate adverse reactions

If signs and symptoms suggestive of a transfusion reaction appear in conjunction with a transfusion, the transfusion *must be immediately interrupted*; the necessary support therapy must be guaranteed, including possible resuscitation maneuvers and treatment of complications, if any, and an immediate report of the detected transfusion reaction must be forwarded to the Transfusion Service, together with a blood sample for immunological tests in order to establish the nature of the transfusion reaction and whether this can be attributed to the transfusion.

Acute hemolytic reactions

They are rare occurrences, due to transfusion of incompatible red blood cells, generally from major incompatibility of the ABO system, following non-compliance with procedures or human error. The onset can vary from a few minutes to some hours after beginning the transfusion and is characterized by the sudden onset of discomfort, fever, nausea, shivers, lower back pains, pain at the venipuncture site (if the infusion is in progress), dyspnea, hemoglobinuria and shock. Acute hemolytic reaction can be complicated by a picture of Disseminated Intravascular Coagulation (DIC) and become fatal.

• Management of acute hemolytic reactions: see *Management of immediate adverse reactions*.

Febrile non-hemolytic reactions

One of the pathogenetic mechanisms responsible for febrile non-hemolytic reactions (FNHTR) is the bond of recipient's antibodies (anti-HLA, anti HPA) with the corresponding leukocyte antigens of the donor, which triggers the release of proinflammatory and pyrogenic cytokines (IL1-b, IL-6, IL-8, TNF), called "biologic response modifiers" (BRM). Another possible cause of FNHTR is the bacterial contamination of the transfused unit. It manifests itself with a fever rise greater than 1°C above the patient's baseline value.

• Management of febrile non-hemolytic reactions: see *Management of immediate adverse reactions*. Febrile non-hemolytic reactions usually respond very well to the use of oral antipyretics; for a more rapid action, intravenous adminstration is recommended. It is useful to perform blood culture of the patient and microbiological control of the unit.

Allergic reactions

They are mainly due to plasma proteins present in the blood component. They can be mild to severe and occur immediately or some time after the transfusion. Minor manifestations include skin symptoms (hives, itch) and are generally mediated by IgE. More severe reactions such as vomit, diarrhea, abdominal pains, angioedema, bronchospasm, hypotension or other symptoms of anaphylaxis may occur in patients with IgA deficiency and anti IgA antibodies.

• Management of allergic reactions: see *Management of immediate adverse reactions*. Occasional mild allergic reactions are responsive to oral antihistamines.

TRALI

This is a serious complication, characterized by a Transfusion-Related Acute Lung Injury: microemboli, endothelial lesions and increased vessel permeability, attributable to immunological (passive administration of anti-HLA antibodies directed against the recipient's leukocytes) and non immunological mechanisms (patient's predisposition, presence of cytokines in the units). The clinical picture is characterized by dyspnea, tachycardia, fever and hypotension that appear during transfusion or within six hours of its completion. There is hypoxemia and the chest x-ray shows bilateral infiltrates typical of pulmonary edema, although there is no true circulatory overload[77].

• Management of TRALI: see *Management of immediate adverse reactions*. The treatment of TRALI requires oxygen therapy, administration of steroids and diuretics and possible resuscitation maneuvers, with assisted ventilation[77].

Circulatory overload

It may occur in the presence of an already known or unacknowledged cardiac dysfunction or when the infusion rate is excessively high. Signs and symptoms

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of cardiocirculatory overload include dyspnea and tachicardia and chest x-ray shows the classical signs of pulmonary edema[44].

- Management of cardiocirculatory overload: see *Management of immediate adverse reactions*. The treatment is based on the administration of diuretics, oxygen therapy and possible positive inotropes.

Management of delayed adverse reactions

If signs and symptoms suggestive of a transfusion reaction appear following a transfusion, the necessary support therapy must be guaranteed, and an immediate report of the detected transfusion reaction must be forwarded to the Transfusion Service, together with a blood sample for immunohematological tests in order to establish the nature of the transfusion reaction and whether it can be attributed to the transfusion.

Delayed hemolytic reactions

They occur 5-14 days after the transfusion and are characterized by anemia, discomfort and jaundice. These reactions can depend on alloantibodies not yet identified before the transfusion, on the production of a new antibody or on a secondary immune response from low-titer anamnestic antibody, present but not detectable before the transfusion[44].

- Management of delayed hemolytic reactions: see *Management of delayed adverse reactions*. A blood sample from the patient must be tested for new antibodies and the pre-transfusion tests on the last units administered must be repeated.

Delayed hyperhemolysis syndrome

Hyper Hemolytic Syndrome (HHS) related to Delayed Hemolytic Transfusion Reaction (DHTR) is a dreadful complication of transfusion therapy in patients with hemoglobinopathies[78-80] and particularly in SCD and NTDT patients. The syndrome can appear from 2 to 20 days after the transfusion session, both after direct transfusion and after erythroexchange[81,82] with an incidence ranging from 4 to 15.2% of patients[83,84] and a significant mortality, reported from 6 to 11.5%[72,83,84] and a time-dependent progression, strictly related to the earliness of the diagnosis.

The HHS-DHTR hyperhemolytic syndrome is underdiagnosed, even up to 40% of cases according to Gerritsma[84], especially in patients affected by SCD, considering that the symptoms of onset, including pain, can mimic the painful manifestations of vaso-occlusive crises related to SCD.

Role of alloimmunization

SCD and NTDT patients have a particular susceptibility to the formation of alloantibodies, often in the form of mixtures of antibodies, both to antigens of the Rh system and to antigens of minor antigenic systems[73]; however, HHS-DHTR not necessarily appears in already alloimmunized subjects: this in fact occurs in 61% of cases, whereas at least one third of the patients who develop HHS-DHTR has NO history of alloimmunization[85]. Finally there is a percentage of patients that is difficult to quantify showing a possible or potential previous alloimmunization, related to anamnestic antibodies not detectable at the time of admission: this is the well-known phenomenon of "antibody evanescence"[72,86]. Furthermore, in a significant percentage of patients with SCD (~30%) it is not possible to identify allo- or autoantibodies during HHS-DHTR.

In addition to this, the onset of HHS-DHTR does not appear to correlate with the degree of matching between transfused units and the patient's blood group system antigens: some Authors report its appearance also in subjects transfused with units assigned with an extended match ABO/RH/Kell/Duffy, Kidd, MNS)[84]; nor does it seem to correlate with the number of transfused units: there are reports of the onset of HHS-DHTR in patients transfused for occasional events and with a limited number of units[80,86].

On the other hand, the history of a previous episode of HHS-DHTR has to be taken into high consideration: 28% of patients have already experienced a previous episode of HHS-DHTR[72,81,86].

Role of the complement

A key role in the pathophysiology of HHS-DHTR is played by the complement cascade, which is over-activated both through the classical, antibody-mediated pathway and above all through the heme-dependent alternate pathway[70,87]. Free heme and hemoglobin, present as free molecules for chronic hemolysis related to the underlying hemoglobinopathy[88], contribute to endothelial and tissue damage[70,88], amplified by the action of complement degradation molecules and by the activation of the inflammatory response and the immune response[88]. Furthermore, heme has a blocking action on factors that regulate the alternate complement pathway such

as properdin or FI, thus favoring the persistence of over-activation in particular of the complement alternate pathway.

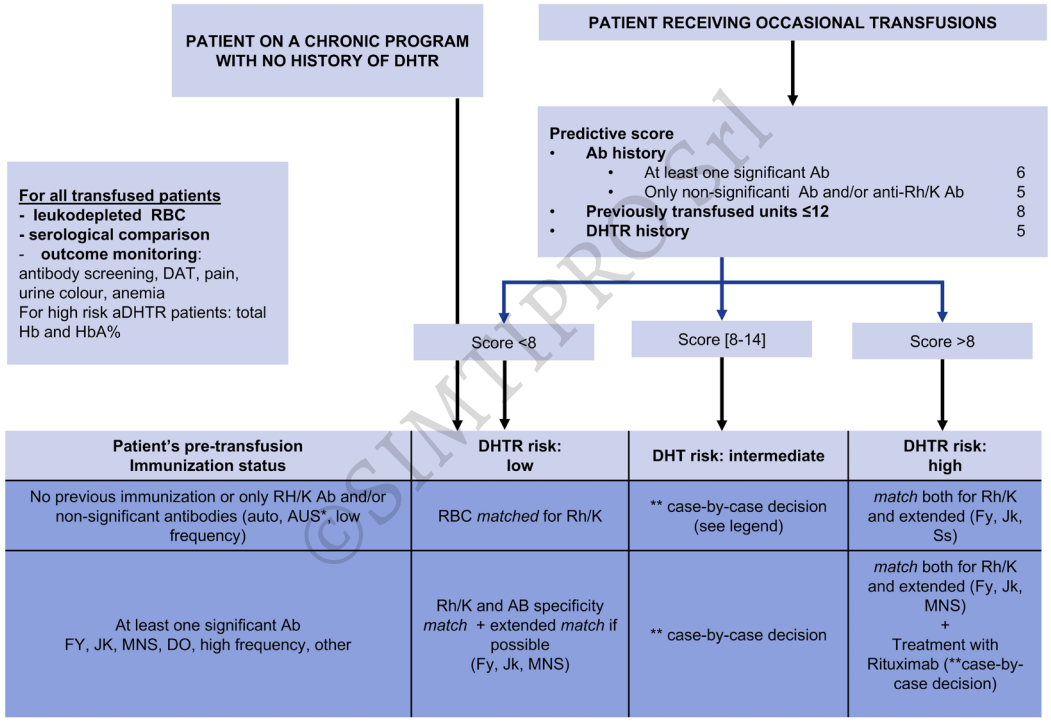
Prevention

The prevention of the onset of HHS-DHTR is fundamentally based on the prevention of alloimmunization, through the assigment of units of erythrocyte concentrates with the best match, in particular for the most immunogenic antigens, taking into account the clinical and transfusion history of the patient, remembering that:

- in 60% of HHS-DHTR episodes the patient is already immunized, and occasional transfusion appears to be associated with a higher incidence of HHS-DHTR onset than continuous chronic transfusion regimens[70];
- in over 25% of cases HHS-DHTR appears in patients who have already experienced a previous episode of HHS-DHTR[72].

A further patognomonic element is represented by reticulocytopenia, due to the complement-mediated macrophage action on erythroid precursors and to the consequent ineffective erythropoiesis[81].

From the clinical experience associated with the patient's anamnestic data, a score indicative of the risk of HHS-DHTR was obtained (**Figure 2**).



Modified from Pirenne and Yazdanbakhsh Blood. 2018;131(25):2773-2781

Figure 2 - DHTR risk calculation[70]

Patients undergoing a chronic transfusion protocol are considered low-risk DHTR. For patients receiving episodic transfusions, 3 scores, resulting from statistical analysis, are considered DHTR risk factors. (**1**) History of red blood cell immunization. A score of 6 is assigned if the patient has a history of at least 1 clinically significant antibody (other than anti-Rh o anti-K) classically known to be involved in transfusion reactions such as anti-Jk^b, Fy^a, S, Hb^S. A score of 5 is assigned if the patient has a history of only anti-Rh/-K antibodies and/or considered non clinically (clin) significant (for example, autoantibodies or non-specific antibodies [Ab]). Therefore, a patient who has an anti-Rh plus an anti-Jkb is assigned a score of 6 (and not 6 + 5). (**2**) Cumulative transfusions of 12 units or less. (**3**) A previous DHTR. By adding the scores, a DHTR risk score is calculated and the transfusion is adjusted accordingly. Patients with a score <8 are considered low risk. Episodically transfused patients who are at low risk for DHTR are transfused with Rh (D, C, E, c, e) and K matched red blood cells, which is extended to Fy, Jk and Ss only of the patient has developed antibodies to any of these antigens.

*AUS, antibody with unknown specificity; **Patients with a score between 8 and 14 have an intermediate risk. For such patients the extent of matching should be based on the history of DHTR and on the number of previous transfusions; those with no history of DHTR who have been transfused only a few times are considered to be at lower risk similar to low-risk patients, but should be monitored closely anyway. However, patients with intermediate DHTR risk who have a history of DHTR and few transfusions in the past (≤12), are generally considered high risk and receive extended matched red blood cells (Fy, Jk, Ss). Patients with a score >14 are considered high risk for DHTR. Episodically transfused patients with a high risk for DHTR (based on the predictive score) always receive extended matched red blood cells (Fy, Jk, Ss). Prophylactic use of rituximab should be considered for patients with a history of alloantibodies and serious DHTR, recently eculizumab has also been used prophylactically when transfusion therapy is necessary.

Diagnosis

It is a difficult picture to recognize and diagnose, especially due to the variability with which it can manifest itself at the onset, but it is probably more common than you might think. HHS-DHTR is suspected in case of appearance, after a recent transfusion (2-15 days), of asthenia, hyperchromic urine (hemoglobinuria), anemia with Hgb values lower than before transfusion (in particular acute loss of at least 1.5-2 g/dL of Hgb compared to the patient's historical control, with Hgb values that can reach also up to 4-6 g/dL), high LDH (up to over 2,000 IU/L), and in SCD the appearance of signs compatible with vaso-occlusive crisis such as muscolo-skeletal pain, fever, asthenia. This is associated with HHS-DHTR in SCD patients in over 80% of cases[70,72,81,84,89].

The elements described are therefore to be considered "red flags" and must alert the doctor to whom the patient refers to promptly start an adequate treatment, before the case can evolve into acute lung injury (ALI) and irreversibly into multiorgan failure[70]. An additional laboratory parameter that can help the diagnosis in SCD is the determination of HbA percentage, which in cases of HHS-DHTR decreases rapidly, due to the "catastrophic" hemolytic cascade that involves not only the patient's own red blood cells, but also recently transfused red blood cells[70,82,90] (**Figure 3**).

Evolution and prognosis

The clinical picture is rapidly evolving: in 50% of the cases the onset of HHS-DHTR can be complicated, resulting in acute chest syndrome or acute lung injury (ALI) or multiorgan failure within few hours[70-72].

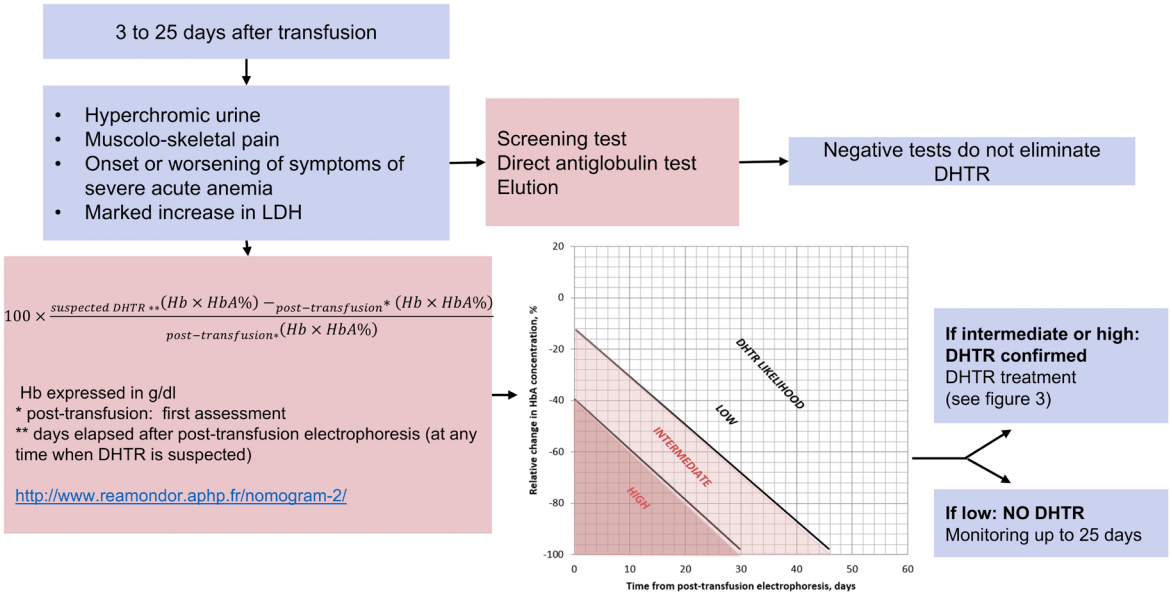
Once again, we remind that this pathology is strongly time-dependent, with a still high mortality.

Treatment

The aim is to reduce and limit the ongoing hemolytic process and to support erythropoiesis, it is based on the following strategies (**Figure 4**):

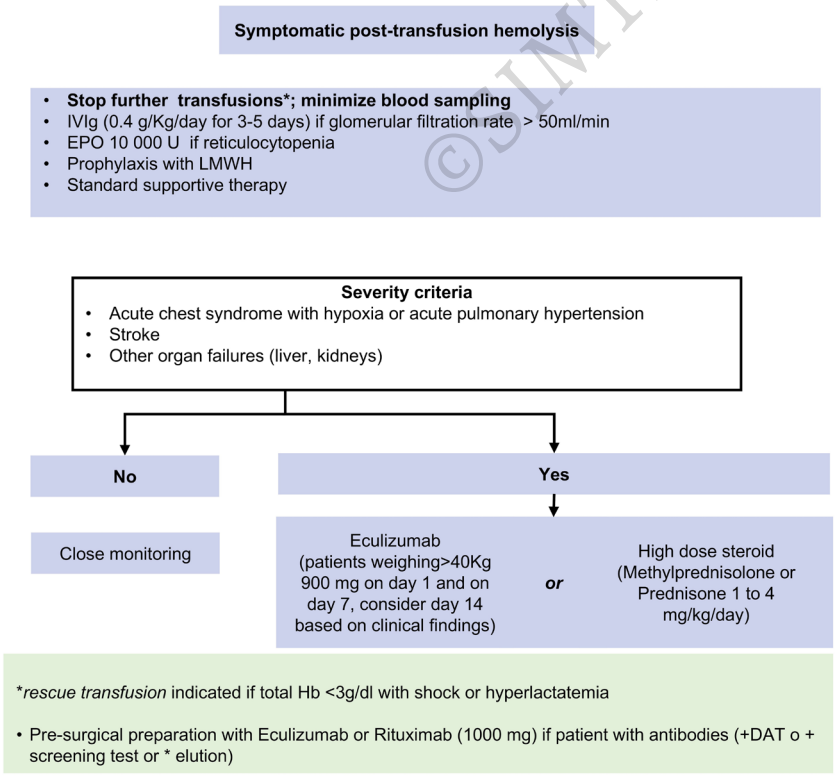
1. EV immunoglobulins (0.4-0.5 g/kg/day for 5 days) and steroid at immunosuppressive dosage, prednisone 1 mg/kg/day, considering that in SCD patients this drug could contribute to an acute worsening of the clinical picture due to the recrudescence of VOCs or the evolution towards even fatal forms such as acute chest syndrome.
2. Eculizumab[73,80,82,87] at a dosage of 900 mg iv for weight >40 kg; 600 mg iv for weight 10-40 kg, 300 mg iv for weight 5-10 kg (1 to 3 administrations 7 days apart based on the clinical evolution). Eculizumab is a monoclonal antibody anti-C5 of the complement, which has an effect on the complement activation systems and whose efficacy seems optimal if used from the onset of HHS-DHTR[80,82]. Until now this seems to be the most promising and interesting therapeutic option in the management of HHS-DHTR associated with SCD[87,91] because it acts directly on the pathogenic mechanism. It also allows to prevent acute organ complications related to heme and free hemoglobin such as renal damage, endothelial damage (hypertensive crisis) and pulmonary damage (ALI).
   - There are no well-controlled studies in pregnant women treated with eculizumab. Data on a limited number of pregnancies exposed to eculizumab (less than 300 pregnancy outcomes) indicate no increased risk of fetal malformations or fetal/neonatal toxicity. However, due to the lack of well-controlled studies, uncertainties remain. Therefore, an individual risk/benefit analysis is recommended before and during treatment of pregnant women with eculizumab. If such treatment is considered necessary during pregnancy, careful maternal and fetal monitoring is recommended, according to local guidelines[91];
   - The use of high-dose steroids can be avoided by using eculizumab.This is positive, considering that steroids can exacerbate vaso-occlusive crises in SCD[70].
3. Erythropoietin (EPO) in presence of reticulocytopenia.
4. Prophylaxis with low molecular weight heparin (LMWH), protective of free heme-mediated endothelial damage.
5. Consider vitamin B12 and folate supplementation (rapidly bioavailable form, e.g., calcium lederfolinate)[73].
6. Eculizumab or rituximab in case a rescue transfusion is required or in preparation for scheduled surgical interventions (e.g., hip replacement).

In the most severe forms, plasma exchange is proposed, but it must be taken into account that the extracorporeal volume of the separator could further reduce the level of hemoglobin and tissue oxygenation[70,73].



Modified from Pirenne and Yazdanbakhsh Blood. 2018;131(25):2773-2781

Figure 3 - Recommended guidelines for the diagnosis of DHTR in adult sickle cell disease patients[70]
Our evaluation criteria for diagnosing DHTR in recently transfused adult SCD patients are based on clinical and laboratory features (pain, anemia, urine colour, elevated LDH) and immunohematological tests, that may or may not reveal the presence of new antibodies. If DHTR is suspected, it is recommended to use the immediate post-transfusion total Hb in g/dL and HbA% following the nomogram shown, to determine the probability that a patient has DHTR. The formula can be calculated directly by using the link provided in the figure.



Modified from Pirenne and Yazdanbakhsh Blood. 2018;131(25):2773-2781

Figure 4 - Recommended treatment for patients presenting with post-transfusion hemolysis[70]
In such cases transfusions must be stopped unless (as indicated by the asterisk) the patient has deep anemia (total <3 g/dL with shock or hyperlactatemia), in which case rituximab is indicated for patents with +DAT or +test di screening or + elution associated with a low dose of methylprednisolone to prevent the steroid from aggravating or triggering a VOC. Symptomatic patients who develop DHTR should be treated immediately with intravenous immunoglobulins (IVIg), adding erythropoietin (EPO) if DHTR is also associated with reticulocytopenia. Administer anticoagulant prophylactic therapy to reduce the risk of thrombosis associated with EPO administration. Supportive therapy is always indicated. If the patient presents severity criteria (acute chest syndrome or acute pulmonary hypertension, stroke or organ failure), additional treatment with eculizumab may be effective in this case, if not vaccinated against meningitis use antibiotic prophylaxis until vaccination is possible.

In SCD patients plasma-exchange could be considered in the acute phase before eculizumab infusion, precisely for the purpose of removing free heme overload.

Transfusion is absolutely advised against in these cases because it increases the risk of exacerbating hemolysis and leading to multiorgan failure[72,73]. Transfusion should be reserved for patients who reach very low hemoglobin values with severe hypoxia: in these cases transfusion should be done with extreme caution, assigning units of erythrocyte concentrate with the phenotypic match closest to that of the patient[70] and strictly monitoring the patient's vital parameters. It is useful and appropriate to have the patient's complete antigenic profile, including minor blood group systems, to identify the erythrocyte concentrate units with the best match for the patient and to guide the identification of the specificity of any alloantibodies.

PREVENTION OF TRANSFUSION REACTIONS

An effective prevention of the main adverse reactions is achieved by following the indications below[44,59]:

- prevention of transfusion errors due to identification mix-ups;
- prevention of febrile non-hemolytic transfusion reactions;
- prevention of allergic transfusion reactions.

Prevention of transfusion errors due to identification mix-up

Identification errors can be avoided by observing the following indications:

- univocal recipient recognition method (active recognition when possible, bracelet, bar code, biometric parameters, etc.);
- active identification, repeated and checked by the patient before transfusing each unit of blood component;
- checking by two operators of the identity of the bag and the recipient before starting the transfusion.

Prevention of febrile non-hemolytic transfusion reactions

To prevent febrile non-hemolytic transfusion reactions, leukodepleted erythrocyte concentrates are administered by removing the leucocytes from the unit, in fact, the release of cytokines is significantly minimized and leucocyte alloimmunization is prevented.

There is no evidence that routine premedication with antipyretics works, and anyway it is not encouraged because it may mask the onset of a febrile transfusion reaction[92,93]; however, other possible signs or symptoms of hemolysis, such as changes in blood pressure, pulse and respiratory rate in hemolytic reactions, are not masked.

Prevention of allergic transfusion reactions

In patients with a history of recurrent allergic transfusion reactions, pre-medication with oral antihistamines or, if insufficient, with systemic antihistamines, can be performed (Grade of recommendation: **3B**). In patients who do not respond to antihistamines, the administration of hydrocortisone one hour before the transfusion can be useful (Grade of recommendation: **3B**).

Premedication should be administered at precise time intervals before the transfusion: in particular intravenous premedications should be administered immediatately before starting the transfusion, whereas oral premedications 30 to 60 minutes before.

In patients who present severe allergic reactions, despite adequate premedication with antihistamines and steroids, it is indicated to transfuse washed erythrocyte concentrates (Grade of recommendation: **3B**).

Patients with IgA immunoglobulin deficiency, who have had a severe anaphylactic reaction or have an ascertained anti-IgA antibody, should receive IgA-free blood components obtained by washing.

MANAGEMENT OF THE FACILITY RESERVED FOR TRANSFUSION THERAPY

The description of the characteristics of the facilities reserved for transfusion therapy applies to the management of transfusion-dependent thalassemia major and intermedia, the management of non-transfusion dependent thalassemia (NTDT), in situations in which transfusion therapy is indicated and in sickle cell disease when transfusion therapy is deemed indicated and appropriate. In the management of patients with sickle cell disease, undergoing erythrocyte exchange procedures performed with an automated method, it is essential that the facility where the patient is being treated can avail itself of a transfusion structure authorized to carry out therapeutic apheresis activities. The care unit must ensure multidisciplinary management, specialized and continuous care and facilitate patient's compliance with long term treatment protocols.

Management and characteristics of the facility[94]

The facility must have at its disposal areas that are adequate in size, lighting and ventilation, reserved and equipped for transfusion therapy and, when required, must refer to a transfusion facility where therapeutic apheresis can be performed.

If children and adults are treated in the same center, it is advisable to create dedicated and separate areas, in order to respect the different needs of the patients (furnishings, recreation room, entertainment, volunteering, presence of parents) and it is necessary to define specific protocols for carrying out erythroexchange procedures in pediatric patients, in particular if they are low weight (<30 kg).

Separate areas must also be provided for the management of patients with acute events (semi-intensive care beds within the relevant department or separate areas of the same facility in case of hospitalization).

Management of the personnel

Collaboration between the medical-nursing team, the patient and his/her family is fundamental to obtain good results in the treatment. Medical and nursing staff should guarantee continuity of care to the patient from pediatric age to adulthood, even though with different organizational methods.

For both types of transfusion support therapy (simple transfusion or erythroexchange) the operating unit must have personnel experienced in the management of transfusion or apheresis procedures (in particular in erythroexchange procedures), ensuring continuous training and updating of the operators, defining the minimum training requirements of the personnel and periodically verifying the maintenance of their expertise.

Management of vascular access

Special care should be given to training nursing personnel in the management of peripheral venous access and central vascular access. The peripheral vascular access infusion device should be such as to allow appropriate flow rates, without causing damage to the vein; the choice depends on the characteristics of the patient's veins, the volume, the rate and the expected duration of the transfusion, as well as on the type of transfusion support: simple transfusion, manual erythroexchange, or apheresis therapy. The use of ultrasonographs for ultrasound-guided finding of deep venous access may be useful.

Apheresis procedures require the positioning of a peripheral vascular access of the largest possible gauge, in order to ensure an adequate blood flow; high blood viscosity (as occurs in patients undergoing erythroexchange, in particular with a sickle cell crisis underway) can severely impede blood flow through the separator and make the procedure extremely difficult. For this reason, it is appropriate to well hydrate the patient before each procedure (10-15 mL/kg of saline solution in the 2 previous hours, subject to the state of hemodynamic compensation).

In pediatric patients and in patients without adequate vascular access, for whom there is an indication for an urgent apheresis procedure, the opportunity to position a central venous catheter must be evaluated. Any central venous catheters (CVC) already present in the patient can be used also for transfusion therapy, but require special attention by the operator to prevent complications related to manipulation: contamination of the connection point with the intravenous line, infection of the cutaneous ostium of the CVC, gas embolism (at the time of opening CVC pathways, or due to rupture of the external CVC line as a result of clamping with a Pean or other inappropriate devices), obstruction/occlusion of the CVC lumen (due to inadequate washing of the CVC lumen upon closure).

In such cases a deep peripheral vascular access found with the aid of ultrasound guidance can also be used for both the sampling and the reinfusion pathway, taking care to keep the end of the device distal to the beginning of the axillary vein for the sampling pathway to ensure good flow (in these cases, since these are deep veins, neither a tourniquet nor a cuff can be used to increase blood flow).

Management of the equipment

The nursing staff must be specifically trained in the use of all equipment present in the facility: infusion pumps, oxygen delivery systems, cell separators. The user manual in its most updated version must always be available for consultation. Each piece of equipment must be certified.

All documents regarding each piece of equipment must be gathered in a specific dossier, available for consultation by nursing and medical staff, by the person in charge of the facility and by the technical staff responsible for maintenance and checks.

Management of complications, adverse reactions and adverse events

There must be appropriate devices and equipment for the detection of vital parameters and the management of any complications, adverse reactions and adverse events. There must be a procedure that defines the intervention modalities in the event of serious adverse reactions and activation of intensive care when necessary (emergency trolley, defibrillator, telephone number for emergency intervention of the intensive care, etc.).

When indicated, the apheresis procedure must be performed with continuous monitoring of vital parameters (ECG tracing, heart rate, oxygen saturation, blood pressure).

ENCLOSURES

Enclosure 1 - Posology and transfusion yield

Indicatively, in adults a unit of erythrocyte concentrate increases Hgb by 1 g/dL and Hct by approximately 3%. **Table I** shows the increases in Hgb and Hct depending on the patient's weight and blood volume.

Table I - *Average increase in Hgb and Hct 24 hours after administration of 1 unit of erythrocyte concentrate for patients >20 kg*

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

Modified from: Recommendations for transfusion strategies in hemoglobinopathies, 2014[1].

In the event of lower-than-expected transfusion yields, it is suggested to also evaluate the presence of occult bleeding, if any, primary or secondary immunological causes, or hypersplenism. In pediatric patients the transfusion of 5 mL/kg causes an increase in Hgb of approximately 1g/dL[10].

To estimate the quantity of concentrated erythrocytes necessary to correct anemia in patients <20 kg, the following formula is reported:

$$Q = (\text{desired Hgb}^* - \text{pretransfusion Hgb}) \times 5 \times P$$

where:

Q = mL of concentrated erythrocytes to be transfused

Hgb = hemoglobin expressed in g/dL

P = patient's weight in kilograms

Enclosure 2 - Perioperative management and prevention of postoperative complications in sickle cell disease

Any major surgery or eye surgery may be complicated by an acute vaso-occlusive crisis or acute chest syndrome (ACS)[95], which may occur in 40-50% of patients undergoing surgery with elevated HbS concentrations. The patient can be operated after adequate preparation, bringing the concentration of HbS <30%[19,23,36,46,89,96].

According to the American Guidelines[23], preoperative transfusion support is recommended for all SCD patients for major surgery (if the surgical technique involves opening of deep fasciae - thoracic, abdominal, joint cavities), or for all interventions involving anesthesia lasting >1 hour[23], always indicated in ophthalmic surgery[36,46,97].

Preoperative patient management

In the preparation of low or intermediate risk surgical interventions, simple transfusion may be sufficient, maintaining the patient's Hgb <10-11 g/dL[23,24,36,89,95,96]. In the preparation of major surgical interventions (in particular cardiothoracic surgery, neurosurgery, ophthalmic surgery) erythroexchanges are recommended[23], with the aim of bringing HbS <30%, to be performed in the 24-72 hours preceding surgery[24,36,46,89,96].

Predeposit autotransfusion is ***always contraindicated*** in these patients, regardless of the patient's hemoglobin level.

In the interventions performed in urgency/emergency situations, if adequate preparation is not possible, simple preoperative and intraoperative transfusion is indicated, associated with copious hydration. In any case it is necessary to determine the preoperative HbS.

Intraoperative patient management

In intraoperative management the following is recommended: adequate systemic hydration, simple transfusion to compensate for any blood loss, prevention of metabolic acidosis, prevention of hypothermia.

The intraoperative autologous blood recovery program is ***always contraindicated*** in these patients.

Postoperative patient management

In postoperative management the following is recommended: adequate hydration, prevention of hypothermia, prophylaxis of infections with full-dose antibiotic therapy and transfusion to correct any blood loss, maintaining Hgb <10-11 g/dL[24,96].

For surgeries performed in emergency situations, without adequate preparation, schedule an erythroexchange procedure within the second-third day, regardless of preoperative HbS value.

Automated erythroexchange procedures performed before the second day may entail a high bleeding risk: if necessary, perform manual exchange.

For elective surgeries, with adequate preparation of the patient, check postoperative HbS value, (on day 1-2) and schedule erythroexchanges (on day 5-7) with the aim of maintaining HbS <30%.

Enclosure 3 - Blood donation, HSCs, organs and tissues

Finally, please refer to SITE Good Practice available at www.site-italia.org, *Management of the sickle cell trait: an opinion by expert panel members.*

Enclosure 4 - Level of recipient - transfusion units matching

- Level 1: *AB0; RhD.*
- Level 2: *C, c, E, e; K, k.*
- Level 3: *Fya, Fyb; Jka, Jkb; M, N, S, s.*

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