LABORATORY TESTING OF PATIENT SAMPLES IN TRANSFUSION MEDICINE

RECOMMENDATIONS issued by the Swiss Transfusion Medicine Association (SVTM) and Swiss Transfusion SRC (B-CH) for healthcare professionals, laboratories and medical institutions on immunohaematological and molecular testing of patient blood samples

Content changes in the current version 4, valid from 01.02.2021

- **Abbreviations used** completed with «LDH, Lactatdehydrogenase», «RhD Rh antigen», «Rh-Phenotype Rh antigens C, E,c, e», «Rh/ K-Phenotype Rh antigens C, E, c, e, K» and «DTT Panel Test cells treated with Dithiotreitol»
- **1.2 Quality assurance system and documentation**: 5. bullet point completed with another bullet point: «It is recommended that anti-D, which is due to prophylaxis, is not listed on the BG card.»
- **1.3 Recording and storage obligation** (new subchapter): According to art. 39 and 40 of the TPA, records according to art. 39 and all important documents must, since 2020, be kept for 30 years [4].

  § 5.4.6 "Documentation" of the Swissmedic guidelines Inspections of blood banks of 17.01.2020 also provides the following guidelines [24]:

  - Guarantee of traceability from the donor (via donation number) to the patient and vice versa over a period of 30 years (preferably by the issuing authority, not only in the patient dossier, this requires feedback to the issuing authority on the transfusion that has been carried out).
  - Specification documents (work instructions, SOPs) for all procedures.
  - Results and interpretation of compatibility testing.
  - Traceability of the materials used (incl. lot number) and test procedures.
  - Successful recalls and look backs
  - Use of IT systems (laboratory systems, patient systems)
- **2.3 Equipment**: first section completed with «Laboratory equipment must be qualified and/or validated.».
- **3 Pre-analytics**: 2 new bullet points: «Immunohaematological tests can be performed during the validity period of the sample (max. 96 hours)» and «The retained samples can usually be stored between 2-8°C for 7 days.»
- **4.1 General**: last bullet point completed with anti-Cw: « If an anti-E or **anti-Cw** enzyme-only antibody is present, Rh/K-compatible pRBC can be released by T&S (see § 6.4)»
- **4.4.5 Direct antiglobulin test** reformulated
- **4.4.5.1 Indications for a polyspecific DAT (preferably in the column agglutination test)** new subchapter and illustration shown new
- **4.4.5.2 Indications for pre-transfusion elution**: new subchapter and additional illustration
- **5.4.1 ABO blood group determination**: additional bullet point: «If the first blood group determination was done by genotyping, the second blood group determination can be done by serology. The serological result should be compatible with the first determination.»
- **5.4.3 Determination of the RhD antigen**: additional bullet point: «If the first RhD determination was done by genotyping, the second RhD determination can be done by serology. The serological result should be compatible with the first determination.»
- **6.4 Antibody identification**: 5. bullet point completed with anti-Cw: «The enzyme test is an additional method that is used predominantly by reference laboratories. Occasionally this may result in the identification of an anti-E **or anti-Cw** “enzyme-only” antibody. In such cases Rh/K-compatible pRBC **(antigen Cw not tested)** can be released by T&S.»

- **7.2.4 Further clarifications for premature babies, newborns and children under 4 months [13;14]**: new title (before: «Indirect antiglobulin test»).
- **7.2.4.1 Testing premature infants, neonates and children under four months [14; 15]**: title deleted
- **7.4 Antibody testing in monoclonal antibody therapy**: 2. bullet point completed with tube method or by using a DTT Panel and Kp^{a}: « If the ABS is negative, **by tube method or by using a DTT Panel**, pRBC (ABO/RhD/Rh-pheno/K/**Kp^{a}** compatible) can be released by type & screen,». 3. bullet point adjusted: «**Alternatifely** ~~if problems occur~~, antigen or genotypically compatible **pRBC (Rh-pheno, K, Kpa, Kidd, Duffy, S), without antibody clarification, can be released according to the T&S procedure** ~~products~~ ~~should be transfused (CM can be positive)~~.
- **8.3 Selection of ABO/RhD in platelet concentrates**: 4. bullet point completed with Intercept and remark in brackets: «When transfusing pathogen-inactivated PC **with Intercept**, amotosalen based, irradiation for Graft-versus-Host Disease prophylaxis is not necessary **(further techniques may be added in the future depending on the approval)**»
- **9.3.2 Selection of ABO and RhD blood groups for massive transfusions**: 2. point of the 2. bullet point adjusted: «Once the acute bleeding has stopped, the transfusion should be switched to RhD-negative pRBC as soon as possible. Alloimmunization should be excluded every ~~24~~ **96** hours if RhD-positive pRBC are continued to be given. An ABS should be performed between 6 and 12 weeks after an incompatible transfusion (see § 6.1)»
- **9.8.1 Transfusions in premature infants, neonates and children under four months [13; 14]**: 1. bullet completed with an additional point: **« Before the first transfusion an AB/D control must be made from a second sample. This ensures a BG and RhD identical transfusion. If not, pRBC of BG O must be administered.»** and 2. point of the 4. bullet point completed with « Serum from the mother containing alloantibodies can be frozen and used if needed for testing antigen-negative pRBC.»
- **9.10 Procedure for and selection of blood products if allergic/anaphylactic transfusion reactions occur and in IgA-deficient patients**: «The association between IgA deficiency **(<70 mg/dl (0.7g/l))** or selective IgA deficiency **(lack of IgA, < 0.05 mg/dl)** in patients (with and without the presence of anti-IgA antibodies) and allergic / anaphylactic transfusion reactions is a controversial topic in the literature [16;17]. In a Swiss study of 15’000 blood donors, a selective IgA deficiency was identified with a frequency of about 1:850 [18]. ~~Low IgA is defined by a plasma concentration of less than 70 mg/dl; deficiency by a plasma concentration of less than 0.05 mg/dl.In the event of a transfusion-related allergic/anaphylactic reaction, the option of investigating whether the patient is IgA-deficient should be considered.~~

  Following a transfusion-associated severe allergic/anaphylactic reaction, clarification of a possible IgA deficiency is recommended.
  Caution: the blood sample should be taken prior to transfusion (plasma/pRBC) and the administration of immunoglobulin.

  The IgA concentration of pRBC and PC products (and the concentration of all other plasma components) can be minimized by “washing”. When IgA deficiency and severe allergic transfusion reactions are combined, the administration of washed pRBC and PC or plasma from IgA deficient donors can be considered as a precautionary measure. In exceptional cases, the latter can be used for transfusions that can be planned well in advance.

~~The administration of washed pRBC/PC or plasma from IgA-deficient donors as a precautionary measure can be considered if an IgA-deficient patient experiences a serious allergic transfusion reaction.IgA-deficient plasma can be obtained from the blood of IgA-deficient donors. The IgA content of pRBC and PC products (and the content of all other plasma components) can be minimized by "washing". Alternatively, IgA-deficient donors can be used in exceptional cases for transfusions that can be planned well in advance.~~

Please contact your blood transfusion service for acquisition of all these special products.»

Abbreviations used

AG	antigen
AIHA	autoimmunohaemolytic anaemia
ABS	antibody screen
B-CH SRK	Swiss Transfusion SRC
BG	blood group
CMV	cytomegalus virus
Column agglutination test	Column agglutination test
COMAL	criteria for the operation of medical analytical laboratories
CT	compatibility testing
DAT	direct antiglobulin test (formerly direct Coombs test)
DTT Panel	Testerythrocytes treated with Dithiotreitol
DVI	D variant VI
EDTA	whole blood anticoagulated with ethylenediaminetetraacetic acid
EFI	European Federation for Immunogenetics
EQC	external quality control
FFP	fresh frozen plasma
HDN	haemolytic disease of the newborn
IAT	indirect antiglobulin test (formerly indirect Coombs test)
IgG	class G immunoglobulins
IQC	internal quality control
K	Kell
LDH	Lactatdehydrogenase
MDAT	monospecific DAT
MPLO	Medicinal Products Licensing Ordinance
NA	Not applicable
NaCl	sodium chloride
PC	platelet concentrate
pRBC	packed red blood cells
QC	quality control
QUALAB	Swiss Commission for Quality Assurance in Medical Laboratories
Rh	Rhesus
RhD	Rh antigen
Rh-Phenotype	Rh antigens C, E, c, e
Rh/K-Phenotype	Rh antigens C, E, c, e, K
SVTM	Swiss Transfusion Medicine Association
TPA	Therapeutic Products Act
TPO	Therapeutic Products Ordinance
T&S	type and screen (blood group determination and antiglobulin test)
WP	weeks of pregnancy
XM	crossmatch

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Editorial

This document was composed in collaboration with the Swiss Transfusion Medicine Association (SVTM) and Swiss Transfusion SRC (B-CH SRK) and revised according to the current state of science and technology.

It provides guidelines for good laboratory practice in immunohaematology and also supports decision-taking in specific clinical situations. Regarding cases not described in this document, it is recommended to consult reference documents and/or the doctor responsible for the transfusion.

Since January 2002, the Therapeutic Products Act has required the establishment of a quality assurance system that conforms to the current state of medical science and technology not only for the manufacture but also for the use of labile blood products (TPO Art. 39, para. 4).

Swissmedic was integrated into the consultation process for the revised version and supports the document. These recommendations describe methods suitable for verifying the compatibility of labile blood products with the recipients. Further minimum requirements in terms of pre-analytics, the ordering and selection of suitable blood components and documentation of the process steps with the aim of ensuring safety in transfusion medicine be defined. These recommendations must be taken into account in the context of pre-transfusion testing and for all processes leading to the dispatch of a product for blood transfusion.

A procedure that deviates from these recommendations may be used if, on the basis of current scientific findings, it can reliably be assumed that the procedure will achieve an outcome that is at least equivalent to the quality and safety objectives underlying the recommendations. These recommendations will also be used as a reference during inspections. Additionally, they will be taken into account when evaluating whether an institution performing transfusions has a quality assurance system that is adequate for the use of labile blood products.

As the competent authority, we would like to thank all the organizations and individuals involved.

SWISSMEDIC, Haemovigilance

These recommendations were drawn up by the expert group “Immunohaematology”

1 Introduction and scope

The use of labile blood products (transfusion) is a complex therapeutic activity demanding professional skills of the staff involved in pre-transfusion testing and blood transfusions.

Persons handling labile blood products, in particular, shoulder a great responsibility preventing serious adverse effects. Although there are no statutory requirements governing pre-transfusion testing, the Therapeutic Products Ordinance (Article 39, para. 4) [1] requires institutions usin labile blood products to establish a quality assurance system for these using labile blood products. The system needs to be in line with current state of medical science and technology. Furthermore, it requires a designated person responsible for haemovigilance. Needless to say the laboratory must comply with the recognized standards for quality assurance systems (COMAL) (ISO 15189 and/or 17025 should be sought).

These recommendations apply to laboratories performing immunohaematological testing for users of labile blood products. They describe the procedure for as well as the scope and nature of tests and their interpretation. Furthermore, they define the administrative steps involved in the identification of samples and blood products and the required laboratory documentation.

The doctor prescribing the transfusion is responsible for the transfusion process. Laboratory management advises the doctor responsible for the transfusion on the choice of blood products in order to ensure the transfusion is carried out in an immunohaematologically competent manner. Laboratory management and nursing staff ensure that the blood products comply with the requirements stipulated in the doctor's prescription (see guidelines for quality assurance in transfusions issued by the Swiss working group on quality assurance in the use of blood products [23]).

Information is provided on the following topics:

- Immunohaematological testing,
- Information on quality management,
- Information on the transfusion of blood products,
- Haemovigilance.

1.1 General transfusion requirements [2]

Labile blood products must be used in accordance with the current state of medical science and technology. The indications for and regulations applicable to the use of the individual blood products are the responsibility of the doctor performing the transfusion. Requirements concerning the following points must be observed:

- Pre-analytics,
- Recipient identification,
- Pre-transfusion immunohaematological testing,
- Documentation and transmission of the results of immunohaematological testing,
- Identification of blood products,
- Traceability of transfused blood products,

The various aspects of the transfusion process must be regulated in internal regulations (in the hospital/clinic/doctor's practice and testing laboratory). The legal stipulations require the designation of a responsible person for haemovigilance [3] should be on the transfusion committee, if one exists.

1.1.1 Preventive antigen testing

In 2017, Swissmedic, the SVTM and SGH declared their agreement with the opinion of the immunohaematology (IH) working group on the following topic:

These recommendations include several patient groups who should receive antigen-matched blood as a preventive measure.

Swiss Transfusion's IH working group has ascertained that there is as yet no decision on whether the pRBC products chosen for prevention actually have to be checked for the antigens in question, or whether testing that is already part of the system as either a single or multiple determination is sufficient.

The IH working group is of the opinion there is no need for a second antigen testing (even though it is aware that in very rare cases mismatches might occur).

This means that only in the presence of antibodies (see § 4.5.2) must the pRBC be antigen-controlled.

1.2 Quality assurance system and documentation [4]

- The laboratory tests, quality controls and laboratory documents must comply with the requirements stipulated in the quality assurance system.
- Laboratory management is responsible for ensuring that:
  - Detailed operating procedures for the tests performed in the laboratory are available to all staff and that they are followed,
  - The laboratory procedures comply with the quality assurance requirements,
  - Any required algorithms and flow charts have been defined.
- Laboratory management approves the laboratory documents. Responsibility for signing them (electronically as well as manually) may be delegated, but delegation must be documented.
- The laboratory documentation comprises:
  - Results and interpretation of pre-transfusion testing,
  - The date and signature/initials of the employee who performed the tests (or an electronic alternative),
  - A list of the labile blood products supplied (product specifications and issue numbers).
- Minimum requirements to be met by the blood group card:
  - Surname, first name, full date of birth,
  - ABO blood group and RhD, including information on any D variants,
  - Case number, date and signature (or electronic alternative),

  - Identified anti-erythrocyte alloantibodies
    - It is recommended that anti-D, which is due to prophylaxis, is not listed on the BG card.
  - The blood group card is not valid until the second blood group determination becomes available (see § 4.1 and 4.2). This information must be printed clearly on the blood group card.
- Expanded requirements to be met by the blood group card:
  - Patients with clinically relevant attributes such as antibodies or RhD variants, should be given a blood group card describing these,
  - If available, Rh/K phenotype and other blood group antigens,
  - Reference to transfusion recommendations as required.
- Identification of the recipient's sample: The identity of the patient must have been determined previously and unequivocally (e.g. on the basis of an official identity document) by the responsible administrative office (hospital/practice).
- Relevant findings (ABO/RhD, other blood group antigens, anti-erythrocyte antibodies, transfusion recommendations and transfused products) should be documented in the patient's medical records, in a laboratory or hospital information system. This is the responsibility of the person requesting the analysis of the sample.

The authors are aware that a national register of patients with alloantibodies would offer improvement potential in this context. The aim is therefore to evaluate the options in detail for implementation of such a register.

1.3 Recording and storage obligation

According to art. 39 and 40 of the TPA, records according to art. 39 and all important documents must, since 2020, be kept for 30 years **[4]**.

§ 5.4.6 "Documentation" of the Swissmedic guidelines Inspections of blood banks of 17.01.2020 also provides the following guidelines [24]:

- Guarantee of traceability from the donor (via donation number) to the patient and vice versa over a period of 30 years (preferably by the issuing authority, not only in the patient dossier, this requires feedback to the issuing authority on the transfusion that has been carried out).
- Specification documents (work instructions, SOPs) for all procedures.
- Results and interpretation of compatibility testing.
- Traceability of the materials used (incl. lot number) and test procedures.
- Successful recalls and look backs
- Use of IT systems (laboratory systems, patient systems)

2 Reagents and equipment

2.1 Reagents (in vitro diagnostics)

2.1.1 General

- The laboratory reagents used should be CE marked.
- Non-CE marked products or reagents produced in house must be validated before use. This must be documented and auditable by the competent oversight authority.
- If no information about quality standards is present, it is recommended that a certificate of analysis be obtained from the manufacturer.
- The reagents must be used as directed in the manufacturer's instructions (package insert). Any deviations from these instructions must be validated and documented.

2.1.2 Cell wash solutions

Buffered NaCl solutions with a pH between 7.0 and 7.5 are used to wash RBC.

2.1.3 Test cells

- For reverse typing in ABO blood group determination

  RBC from groups A1, B and O are used for reverse typing (isoagglutinins) in ABO blood group determination. The use of test cells from group A2 is optional.

- For antibody screen (ABS) and for antibody identification

  The test cell from group O used for ABS and antibody identification must have the following antigens: D, C, Cw, c, E, e, K, k, Kp^a, Fy^a, Fy^b, Jk^a, Jk^b Le^a, Le^b, P1, M, N, S, s, and if possible, Lu^a.

  The antigens C, c, E, e, Fy^a, Fy^b, Jk^a, Jk^b, S and s must be expressed homozygously on at least one cell. Commercial test cells used for ABS must be negative for the antigens Mg, Wr^a and Vw.

  Test cells must not be mixed together.

- Control of the antiglobulintest (Coombs-Control)

  Test cells loaded with human IgG immunoglobulins are used.

2.1.4 Test reagents

For determination of the ABO blood group antigens and the RhD antigen

- Monoclonal anti-A, anti-B and anti-AB test sera are recommended for ABO antigen determination. Monoclonal anti-B test sera must not determine an acquired B antigen.
- For RhD antigen determination, two different monoclonal anti-D test sera that originate from different clones should be used. At least one anti-D reagent must not determine the DVI variant. For neonates: see § 7.3

For determination of the Rh phenotype and K and other blood group antigens

- Monoclonal test sera should be used where commercially available (see also § 5.4.4).

2.2 Quality controls

2.2.1 Internal quality controls

The IQC must comply with at least the following requirements:

- Testing of test cells
  - For reverse typing in ABO determination
    - Once a day or at least when the test is performed
    - Controlling of test cells is done using sera/plasma with known anti-A and anti-B antibodies.
  - For ABS
    - Once a day or at least when the test is performed,
    - The test cells for the ABS should be tested using a weak anti-D (maximum identification limit ≤ 10 ng anti-D/ml) [5].
- Testing test sera
  - For AB/RhD antigen determination
    - Once a day or at least when the test is performed,
    - Controlling of test sera is done with RBC with known AB/RhD antigens.
  - For the Rh/K phenotype (CcEe and K)
    - Once a day or at least when the test is performed,
    - Controlling of test sera is done with RBC with known heterozygous C, c, E, e and K antigens.
  - For determination of other blood group antigens
    - Once a day or at least when the test is performed,
    - One positive, if possible heterozygous, and one negative control per antigen tested must also be set up.
- Verification of the result of the antigen determination carried out by indirect antiglobulin test

  A DAT must be set up in parallel using the same test system to exclude false positive reactions in the IAT.
- Verification of the techniques for the direct and indirect antiglobulin test (tube method)

  Every negative result must be checked using a Coombs-Control reagent.
- Verification of DAT in a gel test

No suitable commercial tests are currently available.

- Checking compatibility testing
  - Once a day or at least when the test is performed,
  - Compatibility testing should be checked using RhD-positive and RhD-negative donor RBC and a serum with known weak anti-D (maximum identification limit ≤ 10 ng anti-D/ml) [6].
- Checking molecular genetic test methods

  Checking is determined by the test method (CE kit or in-house).
- Checking all techniques

If analyses are performed using several methods/ techniques, each one should be checked separately.

2.2.2 External quality controls

Laboratories that perform immunohaematological work are obligated to take part four times a year in EQC for immunohaematology organized by a recognized inter-laboratory testing laboratory (see QUALAB); this must cover all analyses for which an EQC is available.

Laboratories that perform molecular genetic testing are obligated to take part in corresponding EQC twice a year. (see § 11).

2.3 Equipment

Laboratory equipment must be qualified and/or validated. The laboratory equipment used for immunohaematological testing must be maintained regularly. The laboratory equipment must be monitored in compliance with the internal quality assurance system and the findings must be recorded and archived in accordance with the current requirements.

Thermally controlled equipment used for blood products (refrigeration units, freezer units, platelet shakers, FFP thawing equipment) must be operated according to the requirements issued by Swissmedic or cantonal authorities.

3 Pre-analytics

- A native blood sample (without separating agent) and/or an EDTA blood sample should always be requested for immunohaematological work.
- The person taking the blood sample confirms in an eligible/appropriate manner (signature/initials on order form and/or tube, reading into an electronic recording system etc.) that the patient has been identified correctly. The laboratory must be able to verify this information.
- Blood samples for immunohaematological testing should, if possible, not be taken from a venous access for drugs, infusions or transfusions (risk of dilution). If this is not possible, care must be taken to ensure that a large enough volume of blood is discarded before sampling to ensure that the sample is not diluted.
- All sample tubes must be labelled in such a way that they can be assigned unequivocally to the patient:
  - Surname, first name, full date of birth, or
  - Unique patient identification number,
  - For umbilical cord blood, the child's identity must be used (name, date of birth).
- The date and time at which the sample was taken must be shown for each tube (tube and/or order form and/or laboratory information system).
- Pre-transfusion testing must not be carried out with blood samples that are not labelled or not assignable.
- If blood samples are not labelled correctly but still assignable, it is the responsibility of the person in charge of the laboratory to decide whether testing can be carried out. Aberrations must be documented.
- Immunohaematological tests can be performed during the validity period of the sample (max. 96 hours).
- The retained samples can usually be stored between 2-8°C for 7 days

4 Pre-transfusion immunohaematological investigation [6]

4.1 General

- Pre-transfusion testing is performed to avoid haemolytic transfusion reactions.
- It includes:
  - Two full blood group determinations (typing) (see § 4.3),
  - Antibody screening (ABS),
  - Compatibility testing of the patient's serum sample with the blood products using T&S (standard method) or crossmatch (XM).
- The blood group of the blood unit must be checked.
- The blood group of the patient and the pRBC must be compatible.
- XM must be performed if clinically relevant alloantibodies are present or relevant alloantibodies are known but currently not detectable (see § 6.4).
- If an anti-D is present: if Rh prophylaxis has been given and clinically relevant antibodies have been excluded, pRBC can be released by T&S (see § 6.4).
- If an anti-E or anti-Cw enzyme-only antibody is present, Rh/K-compatible pRBC can be released by T&S (see § 6.4).

4.2 Sampling and other requirements

Principle:
- Secured verification of patient's blood group confirmed by the presence of two documented, valid blood group determinations,
- Presence of a valid antibody determination (see § 4.3).

- If the blood group is not yet known, a full blood group determination should be performed with two blood samples obtained independently of each other with independent patient identification in each case in order to avoid any mix-ups.
- If only one valid blood group determination is available (internal/external), a second full blood group determination must be performed. Foreign documents must be clearly legible and validated by the person responsible for the laboratory.
- For planned interventions it is recommended that the first blood sample should be taken before the patient is admitted to hospital, for example (blood group determined with simultaneous ABS if appropriate); the second sample should be taken when the patient is admitted, for example (blood group determination, possibly ABS and/or retain sample).
- If two documented full blood group determinations (see § 5.1) or a valid blood group card with two entries are available, it is sufficient to check AB/RhD antigen.
- Deviations from the above procedure are the responsibility of the doctor performing the transfusion and must be documented (see also § 9.2).

4.3 Validity of antibody screening and compatibility testing (for neonates and children < 4 months see § 9.8.1)

- For pre-transfusion investigation using T&S or XM as well as if clinically relevant alloantibodies are present (see § 6.4), the blood sample must be taken less than 96 hours prior to transfusion (extension for pregnant women: see § 7.1.2).

  The transfusion must have started within 96 hours after the sample has been taken.
- After the expiration of the validity of the CT sample, a reasonable effort must be made to investigate the presence of potentially newly formed antibodies. Minimum requirement: Exclusion with test cells being homozygous for Rh, Fy, Jk, S and s, or ensure antigen-compatible transfusion. Known antibodies must be taken into account.
- In pregnant women, if a potentially urgent indication for transfusion exists over an extended period (e.g. placenta praevia), the validity of the ABS can be extended to 7 days (however, two documented full blood group determinations or a valid blood group card must be available, see § 4.2 and 7.1.2).
- For patients who have not received a transfusion in the past three months and those who are not pregnant, the validity of a negative ABS can be extended to 21 days. In this case:

  a) The ABS must be performed by the laboratory, or at least under the responsibility, of the laboratory at the hospital in which the patient receives the transfusion.

  b) At the latest by the time the first request for blood is sent, the transfusion laboratory must have received a document initialled by the responsible doctor, confirming that the patient has not received a transfusion in the meantime (since the sample was taken) and that the patient is not pregnant. If this confirmation has not been received, the result of the ABS is only valid for 96 hours, i.e. an extension of its validity to 21 days is not in conformity with the recommendations (see also § 4.4 and 4.6.2).

4.4 Methods

4.4.1 Blood group determination and antibody screen [7]

- See § 5 and 6.

4.4.2 Release of pRBC for transfusion by type & screen

- Determination of the ABO blood group antigens and the RhD antigen (type).
- ABS to identify anti-erythrocyte antibodies (screening),
- AB/RhD antigen testing of pRBC,
- Verification and documentation of the compatibility of the patient's ABO/RhD with the ABO/RhD of the pRBC.

4.4.3 Electronic release of pRBC for transfusion by type & screen

If the release is performed electronically, the following conditions must be fulfilled:

- The system must adhere to the national recommendations and must be validated,
- A manual backup system must be available in case the electronic system is not available,
- These points must be recorded in writing (e.g. documented in an SOP),

- If there are discrepancies in the blood group and/or antibody determinations, the electronic release may not be performed until these have been resolved.

4.4.4 Release of pRBC for transfusion on the basis of crossmatch

- Determination of the ABO blood group and the RhD antigen,
- ABS to identify anti-erythrocyte antibodies,
- XM of patient serum/plasma with each pRBC using IAT,
- AB/RhD antigen testing of pRBC,
- Compatibility testing:
  - of the patient's ABO/RhD with the ABO/RhD of the pRBC,
  - of any alloantibodies that the patient may have with the correspondingly antigen-negative pRBC.

4.4.5 Direct antiglobulin test

The DAT is used for the detection of antibodies and complement factors which have bound in vivo to the own and/or transfused erythrocytes (e.g. erythrocyte autoantibodies, alloantibodies after transfusions or HDN)

4.4.5.1 Indications for a polyspecific DAT (preferably in the column agglutination test):

s. figure 4.4.5.1

- Pretransfusions < 14 days
- Transfusion reaction
- Signs of haemolysis (e.g. LDH, bilirubin and haptoglobin)
- Suspicion of autoimmune haemolysis (see § 9)
- Suspicion of HDN (incl. BG incompatibility) (see § 7)

- If the DAT is negative, no further steps are recommended.
- If a DAT is positive but not indicated, no further clarification is recommended. This also applies if the transfusion history is unknown. The responsibility for notifying the laboratory of a pre-transfusion < 14 days lies with the responsible doctor.
- If the result is positive, a monospecific DAT (IgG/C3d) should be performed (see Figure 4.4.5.2). An extended monospecific DAT (IgM/IgA) is recommended if signs of haemolysis are present.
- If signs of haemolysis are present, an elution is always performed, regardless of whether the poly-DAT is positive or negative. However, this must only be carried out pre-transfusion if the indications in 4.4.5.2 apply.
- If C3d alone is detected for the first time in the monospecific DAT, cold agglutinins, drug-induced antibodies or delayed haemolytic transfusion reactions due to alloantibodies should be considered for differential diagnosis.
- For emergency situations see § 9.2

4.4.5.2 Indications for pre-transfusion elution

- pre-transfusions < 14 days

- Transfusion reaction

If the DAT is positive and at least one of the two indications is present, an elution is performed pre-transfusion under the following conditions (s. figure 4.4.5.2):

- First detection of IgG-DAT with a reaction strength of ≤ 2+
- Previously known positive IgG-DAT with a significant increase in the reaction strength from previously +/- or (+) to currently 2+. An increase from 1+ to 2+ is not considered significant, no elution is required
- In case of newly positive C3d-DAT without the presence of cold agglutinins
- For each transfusion reaction with signs of haemolysis, an elution is always performed, regardless of whether the poly-DAT is positive or negative
- If clinically relevant alloantibodies are detectable in the eluate, these must be taken into account (XM and antigen neg.), otherwise EK can be released with the T&S procedure
- Pre-transfusion elution is not necessary under the following conditions:
- Known IgG with a constant or decreasing reaction strength
- Known bound IgG with a reaction strength of >2+
- Known positive C3d-DAT (independent of the reaction strength).

Diagram 4.4.5.1

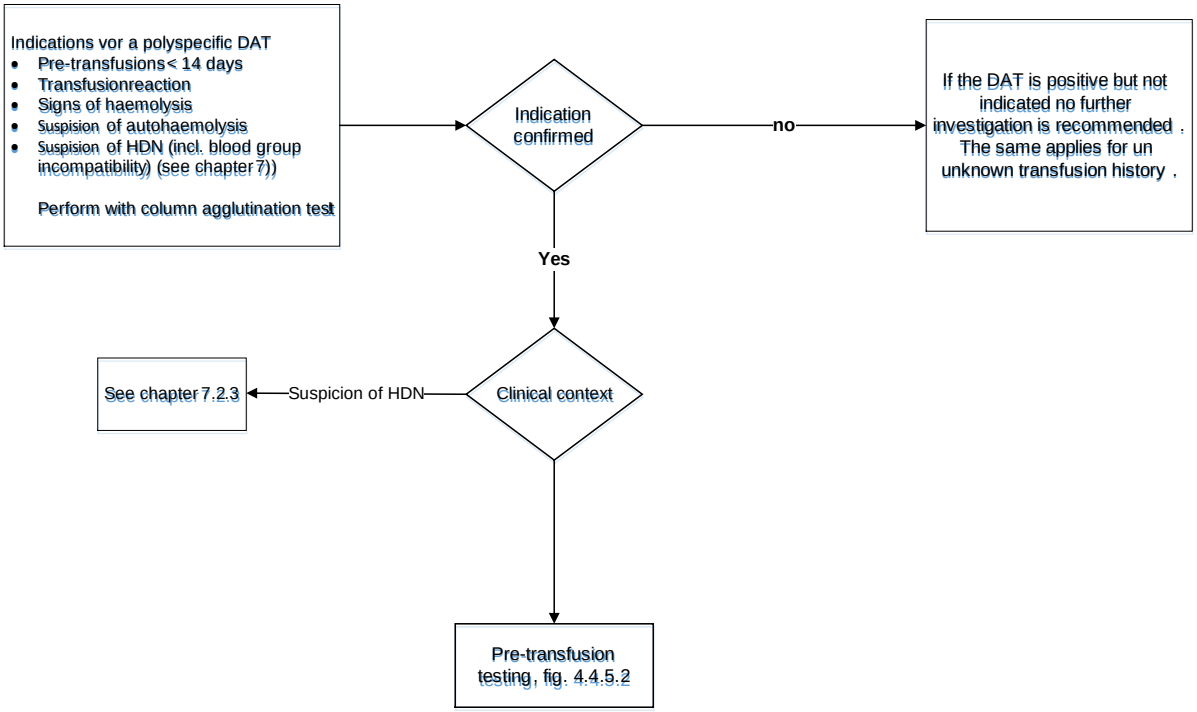
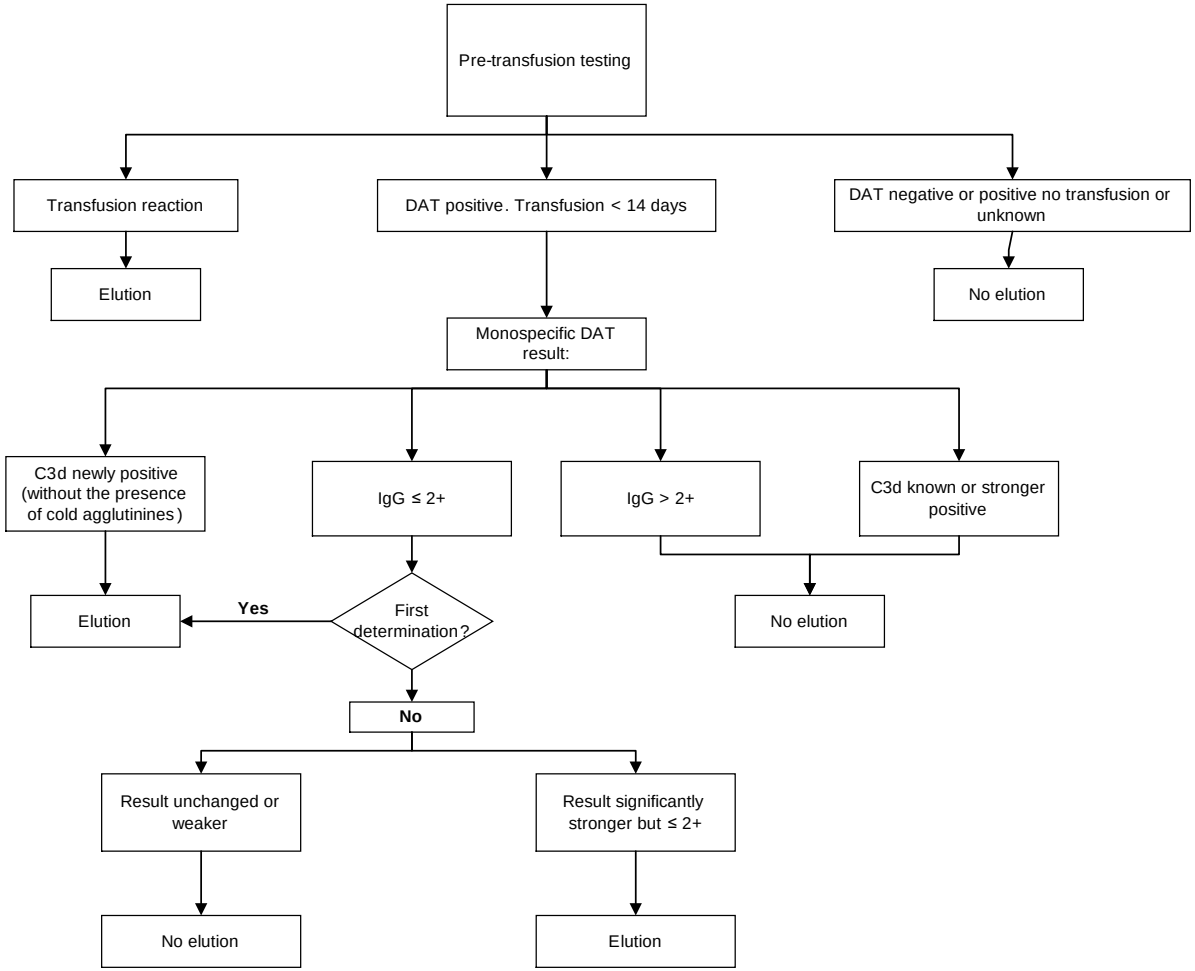


Diagram 4.4.5.2



4.5 Conditions for release

4.5.1 For type & screen

- If the ABS is negative, ABO- and RhD-identical or compatible pRBC can be released for transfusion (see § 8.1.1 & 8.1.2).
- If the ABS is positive, the anti-erythrocyte alloantibodies must be identified (see § 6).
- If transfusion-relevant alloantibodies are present, the T&S procedure must be stopped and XM must be performed (see § 4.5.2). This also applies to known clinically relevant antibodies that are no longer detectable.
- If the results of antibody identification are doubtful or unclear, XM must be performed.

4.5.2 For crossmatch

- If transfusion-relevant alloantibodies are present, XM must be performed with the corresponding antigen-negative pRBC. The pRBC must be tested for the absence of the respective antigens before they are transfused.
- If transfusion-relevant alloantibodies are known but no longer detectable, XM must be performed with the correspondingly checked antigen-negative pRBC.
- If XM is negative, the tested pRBC can be released for transfusion (including, for example, if antibodies to private antigens are present).
- If XM is positive, further investigations must be performed before products are transfused. The doctor responsible for the transfusion must be informed about blood products which are to be released for transfusion with or despite positive XM and about the possible repercussions and precautionary measures. This communication must be documented, stating the names of those involved. If the responsible doctor is not informed because the findings are not clinically relevant, this decision and the name of the person who took the decision must be documented.

4.6 Written information, issue of pRBC, traceability

4.6.1 Written information on accompanying documents

- If pRBC are released for a specific patient, at least the following must be present:
  - Recipient's surname, first name and full date of birth
  - Recipient's ABO blood group and RhD antigen
  - Number of blood unit ABO blood group and RhD antigen of the pRBC,
  - To be transfused by [date]
  - Date and signature/initials of the employee who performed the tests

4.6.2 Issue of released pRBC

- Documentation of the date and signature/initials of the employee who issued the pRBC.
- When the 96-hour rule is applied, the released pRBC (T&S and XM) must be transfused within 96 hours (see § 4.3) after blood sampling. The transfusion must have started within 96 hours after the sample was taken. After this time has elapsed, a fresh sample of the patient's blood must be obtained for repeat pre-transfusion testing (with XM: blood group check, ABS and XM; with T&S: blood group check and ABS) before further transfusions can be performed.

4.6.3 Traceability

- <u>Documentation</u>
  - Identification of the patient's blood samples used for pre-transfusion testing (surname, first name, full date of birth, sampling date and time),
  - Test results of pre-transfusion analyses
  - Numbers of units of the blood products supplied for the patient
  - Date and signature/initials of the employee who performed the tests
- <u>Retain samples</u>
  - A blood sample from the patient and a sample of the pRBC supplied (e.g. segment or blood bag) must be retained in the laboratory for at least 7 days.
  - If the 21-day rule for T&S is applied, it must be ensured that the retained sample (serum or plasma) is kept until day 28.
  - If the serum is kept longer than 7 days it must be frozen.

5 Blood group determination

5.1 Definitions – General

- See § 2.1.3 and § 2.1.4 for the requirements for test cells and test sera.
- Full ABO/RhD blood group determination comprises:
  - ABO antigen determination of patient's RBC and reverse typing using patient's serum/plasma
  - RhD antigen determination
- A 'bedside test' cannot replace regular blood group determination.
- The AB/RhD check comprises AB/RhD antigen determination of the patient's RBC (see also § 4.2).
- Determination of the Rh/K phenotype covers the antigens C, c, E, e, K.
- Determination of other blood group antigens is performed according to § 5.2.3.
- For neonates: see § 7.2.
- If serological determination of ABO/RhD or other blood group antigens is not possible, or if the results are not clear, molecular genetic methods may be used (s. § 11).

5.2 Serological methods

5.2.1 Full blood group determination ABO/RhD

- ABO antigen determination is performed using anti-A and anti-B test sera. The use of anti-AB test sera is optional.
- RhD antigen determination is performed with two different anti-D test reagents (s. § 2.1.4)
- Reverse typing is performed with A1, B and O test cells. The use of A2 test cells is optional.
- <u>Manual determination</u>
  - ABO antigen determination and reverse typing should be performed by two different staff members. If the determination is done by only one person, the antigen determination must be checked using the same sample in a second test (new suspension).
  - RhD antigen determination should be performed by two different staff members. If the determination is done by only one person, the antigen determination must be checked using the same sample in a second test (new suspension).
  - Reverse typing is performed with A1, B and O test cells. The use of A2 test cells is optional.
- <u>Automated determination</u>
  - Automated determination comprises determination using an automatic analyzer and electronic data transfer to a laboratory information system.
  - If ABO/RhD antigen determination and reverse typing (full blood group determination) are performed using an automatic analyzer, testing according to § 5.1 is sufficient.

5.2.2 AB/RhD antigen check

In order to check the AB/RhD antigens it is sufficient to determine them using an anti-A, anti-B and Anti-D test serum.

5.2.3 Rh/K phenotype and other blood group antigens

The minimum requirement is determination using the corresponding test sera and one method.

5.3 Molecular genetic methods (see § 11)

Post-millennial molecular genetic methods have developed into an important supplementary element of blood group diagnostics for patient (recipient) samples.

They are used primarily in situations such as:

- Correct identification of weak D types 1, 2 and 3 for the provision of girls and women of childbearing age
- Determination of the original recipient blood group from samples from previously transfused patients
- Determination of blood group antigens in patients with positive DAT
- Identification of alloantibodies, particularly against rare blood group antigens
- Broad genotyping of donors (not part of these recommendations)
- In the context of haematopoietic stem cell transplantation

In general, CE-marked commercial kits must be used for molecular genetic determination of blood groups. If no commercial kits exist, validated in-house methods can be used.

Section 11 describes the standards for molecular blood group typing.

5.4 Results – Interpretation

5.4.1 ABO blood group determination

- The results of blood group determination and their interpretation are shown in Table 5.4.1. The blood groups must be documented in the simple form “O”, “A”, “B” or “AB”.
- If deviating or questionable results are obtained, the blood group must not be interpreted. Further investigations must be performed (s. § 11).
- If the first blood group determination was done by genotyping, the second blood group determination can be done by serology. The serological result should be compatible with the first determination.

Table 5.4.1 Test results and interpretation of ABO blood group determination

Agglutination of patient's RBC with test serum			**Agglutination of patient's serum/plasma with test cell**				**Interpretation**
Anti-A	Anti-B	Anti-AB*	A_1	A_2*	B	O	blood group
-	-	-	+	+	+	-	O
+	-	+	-	-	+	-	A
-	+	+	+	+	-	-	B
+	+	+	-	-	-	-	AB

***** optional

5.4.2 Result of AB/RhD antigen check

- The results must be consistent with the documented full blood group determination.
- If the results of the AB/RhD antigen check are discrepant, a full blood group determination of ABO and RhD must be done with a new blood sample.
  Important note: All possible errors must be taken into consideration, especially previous or current mix-ups of tubes and/or patients. Since several patients may be affected at the same time, the investigations must be performed as a matter of urgency and the issue of further blood products that may potentially be involved must be postponed.
- If the patient is known to have a weak D (investigated), a serologically negative result in the tube test is not a contradiction. If RhD negative status was documented in the past (before 2012; non-differentiated weak D/RhD variant), a positive RhD result does not represent a deviant result.

5.4.3 Determination of the RhD antigen

- The results of RhD determination and their interpretation are shown in Table 5.4.3.
- If anomalous or questionable results are obtained, the RhD antigen must not be interpreted. Further investigations must be performed (see § 11).
- If the first RhD determination was done by genotyping, the second RhD determination can be done by serology. The serological result should be compatible with the first determination.

Table 5.4.3 Test results and interpretation of RhD determination

Agglutination of patient's RBC by			**Interpretation of RhD**
First anti-D test serum	**Second anti-D test serum**	**Rh control serum**	
positive	positive	negative	positive
negative	negative	negative	negative
weak positive	weak positive	negative	weak D*
XX	XX	negative	weak D / partial D
neg / pos	neg / pos	positive	not possible, investigate

* Transfusion recommendations and during pregnancy: see § 7.2 and 8.1.2.

XX Different results (according to manufacturer's instructions)

5.4.4 Determination of the Rh/K phenotype and the other blood group antigens

- The results must be clearly positive or negative.
- If anomalous or questionable results are obtained, the blood group antigens must not be interpreted. Further investigations must be performed (s. § 11).
- Molecular genetic determination of the major blood group antigens should be considered for patients who have recently received a transfusion (s. § 11).

5.4.5 Anomalous/non-interpretable results

If the results are unclear, further serological and/or molecular genetic methods should be used (s. § 11).

5.5 Data entry

- Manual data entry
  - The data entry should be checked, documented and initialled by a second person.
- Electronic data transfer
  - Correct data transfer must be verified beforehand by validation.

5.6 Release

Results, whether determined manually or automatically, cannot be released until they have been validated.

6 Antibody screen and antibody identification

6.1 Definitions – General

- Potential anti-erythrocyte alloantibodies that are present are identified in serum/plasma or eluate by means of ABS.
- If the ABS is positive, identification of the anti-erythrocyte alloantibodies is performed.
- The investigation of anti-erythrocyte alloantibodies must cover at least IgG-class warm alloantibodies.
- Furthermore, following homologous transfusions of pRBC, it is recommended that a test be carried to check whether alloantibodies are forming. Since certain antibodies are not detectable until several weeks later, and others can rapidly fall below the limit of detection, this follow-up should preferably be done 6 to 12 weeks after the transfusion.

6.2 Methods for the ABS and antibody identification

- The selected method must be equivalent to the tube method in the two-stage IAT with monovalent or polyvalent anti-human globulin serum.
- The patient's serum/plasma or eluate is set up against group O test cells with known blood group antigens at 37°C (see also § 2.1.3).
- Sensitivity and specificity must be at least equivalent to an identification limit of ≤ 10 ng (0.05 IU) anti-D/ml.
- Additional methods, e.g. enzyme tests, may be used.
- It is advisable for the laboratory that investigates the alloantibodies to perform at least an AB/RhD check using the same sample tube.

6.3 Results of the ABS

- ABS negative: no further investigations
- ABS positive: see § 6.4

6.4 Antibody identification

- If possible, alloantibodies should be confirmed with at least two and preferably three antigen-positive and three antigen-negative test cells.
- If possible, an identified alloantibody (caution: previous transfusions) should be rendered plausible by the absence of the corresponding antigen on the patient's RBC.
- Identified alloantibodies must be taken into account according to their relevance for transfusion medicine [6].
- Alloantibodies with the specificities anti-A1, -H, -H(I), -P1, -Le^a, -Le^b, -M and -N are normally not relevant provided that they are only cold- or enzyme-active (negative results in the agglutination test at 37°C and/ if the result is negative in IAT).
- The enzyme test is an additional method that is used predominantly by reference laboratories. Occasionally this may result in the identification of an anti-E or anti-Cw "enzyme-only" antibody. In such cases Rh/K-compatible pRBC (antigen Cw not tested) can be released by T&S.
- Known but no longer detectable antibodies in the ABS: see § 4.5.2.

- If an anti-D is present: if Rh prophylaxis has been given and clinically relevant antibodies have been excluded, pRBC can be released by T&S.
- The exclusion of clinically relevant alloantibodies in the presence of detectable anti-D must be done with RhD-negative test cells that have the same criteria as the test cells used for the ABS (see § 2.1.3). This does not apply to the antigens C and E, which must only be present in heterozygous form on the test cells.

6.5 Minimum requirements for selecting pBRC if antibodies are present.

Please contact the reference laboratory if the antibody in question does not appear in the table below.

	Environment				
Antibody	NaCl	Enzyme only	ID/IAT	AB no longer detectable	Rh/Kell phenotype
ABO					
Anti-A1	T&S	T&S	AG-neg and XM -neg	T&S	♀<50 years old
Rh					
Anti-D prophylaxis	NA	T&S	T&S	T&S	♀<50 years old
Other anti-Rh	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	Yes
Kell					
All anti-Kell	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	Yes
Kidd					
All anti-Kidd	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	Yes
Duffy					
All anti-Duffy	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	Yes
MNS					
Anti-M, anti-N	T&S	NA	AG-neg and XM -neg	T&S	♀<50 years old
Anti-S, anti-s, anti-U	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	AG-neg and XM -neg	Yes
Lewis					
Anti-Le^{a}, anti-Le^{b}	T&S	T&S	XM -neg	T&S	♀<50 years old
P1PK					
Anti-P1	T&S	T&S	XM -neg	T&S	♀<50 years old
Lutheran					
Anti-Lu^{a}	T&S	NA	XM -neg	T&S	♀<50 years old
Anti-Lu^{b}	AG-neg and XM -neg	NA	AG-neg and XM -neg	AG-neg and XM -neg	Yes
Diego					
Anti-Wr^{a}	T&S	T&S	XM -neg/AG-neg, T&S	T&S	♀<50 years old
Yt					
Anti-Yt^{b}	T&S	NA	XM -neg	T&S	♀<50 years old
Other AB					
Anti-Bg	NA	NA	T&S	T&S	♀<50 years old
Anti-HTLA	NA	NA	T&S	T&S	♀<50 years old
Anti-HI	T&S	T&S	AG-neg and XM -neg*	T&S	♀<50 years old
Anti-I	T&S	T&S	T&S	T&S	♀<50 years old
Auto AB in IAT	NA	NA	T&S	T&S	Yes
AB against the stabilizing solution	T&S	T&S	T&S	T&S	♀<50 years old

***** **ABO identical blood**

****** **Anti-E and anti-Cw enzyme AB only: see § 4.1 and § 6.4**

Abbreviations:

- AG-neg and XM-neg: transfuse antigen-negative blood that matches the antibody and tests negative in the XM
- NA: not applicable
- XM-neg: transfuse blood that tests negative in the XM
- T&S: transfuse blood using type & screen
- ♀<50 years old: women from birth to the age of 49

7 Procedure for specific immunohaematological results

7.1 Pregnancy [8;9;10]

7.1.1 Blood group determination and antibody screen

- For regular blood group determination and ABS: see § 5 and 6.
- At the first pregnancy check-up:
  - ABO/RhD is determined if not already known,
  - An ABS is always performed, irrespective of the RhD, between the 10th and 16th weeks of pregnancy [8;9] and in the 28th week of pregnancy [8].
- The Rh/K phenotype is determined if there is a potential need for transfusion.
- RhD-negative pregnant women are given Rh prophylaxis [23].
  - Rh prophylaxis is not necessary if the following exceptions apply:
    - Foetuses with an *RHD*-negative genotype,
    - Neonates with a negative RhD antigen determination (see § 7.3.2).
- RhD variants [11; 13] in pregnant women:
  - Pregnant women with weak D / partial D who have only been investigated serologically are considered to be RhD negative and are given Rh prophylaxis,
  - Pregnant women with weak D type 1, 2 or 3 (molecular genetic determination, see § 11) are considered to be RhD positive. In these cases, Rh prophylaxis should not be given.
  - Pregnant women with other weak D types or with partial D types are considered to be RhD negative and are given Rh prophylaxis (Table 7.1.1).

Table 7.1.1 RhD prophylaxis and PCR

	Weak/partial D RhD not investigated by PCR	**Weak D type 1, 2, 3 investigated by PCR**	**Other weak/partial D investigated by PCR**
Rh prophylaxis If pregnant	Yes, until the result of PCR is available	No	Yes

7.1.2 Antibody specification and antibody titration

- If the result of the ABS is positive, alloantibody identification is performed (see § 6).

- If alloantibodies relevant for the pregnancy are present, it is recommended to test the child's father for the respective antigen.
- Titre determination of transfusion-relevant alloantibodies is recommended during pregnancy.
- The titration should always be performed using the same method and, if possible, in the same set-up as the sample stored when the previous investigation was done (retain sample).
- The samples should be kept frozen until the end of the pregnancy (retain samples). Although the recommended interval for the ABS in pre-transfusion testing of pregnant women is also 96 hours, this can be extended to 7 days in exceptional cases if there is a potentially urgent indication for transfusion that persists for an extended period (e.g. placenta praevia). Antibody screening is repeated after 96 hours prior to elective interventions. In an emergency, the ABS does not have to be repeated, but two documented full blood group determinations must have been performed and (if not done recently) an AB/RhD antigen check must be performed prior to transfusion (see § 4.3 and 4.6.2).

7.2 Testing of neonates and children under four months

7.2.1 Blood samples

- The following samples can be used to determine blood groups and for DAT:
  - Umbilical cord blood,
  - Capillary/venous blood.
- If the results obtained from umbilical cord blood are unclear, the RBC should be washed with buffered NaCl solution or the determination should be repeated with capillary or venous blood. If the results are still unclear, the sample should be sent to a specialized laboratory.

7.2.2 Determination of ABO and RhD antigen

- Determination of the ABO blood group/RhD is done using RBC. No reverse typing is performed.
- The first ABO and RhD determination are each performed with two different test sera (in a double-set-up with at least one different clone each). If the results are weak positive, DAT must be done to exclude false positive results.
- One of the two RhD test sera used must identify the DVI variant.
- Umbilical cord blood may only be used for the first blood group determination. The results must be clear.
- A blood group card is not issued.

7.2.3 Direct antiglobulin test

- DAT must be performed if HDN is suspected.
- If DAT is ≥2+ positive and/or signs of haemolysis are present, elution should be performed to identify the alloantibodies involved.

- An ABS is also performed with a sample of the mother's blood. If no blood from the mother is available, an ABS must be performed with a sample from the neonate (see § 9.8.1).

7.2.4 Further clarifications for premature babies, newborns and children under four months[13;14]

- Testing is performed with the mother's blood and the blood of the child being transfused.
  - Tests performed with the mother's blood: ABO/RhD, ABS
  - Tests performed with the child's blood: ABO/RhD, DAT
  - If the mother's blood is not available and DAT is positive, an ABS and/or elution could additionally and exceptionally be performed with the child's blood.

7.2.5 Results

- If RhD determination of the neonate shows a positive result for RhD, weak D, partial D or an unclear result, Rh prophylaxis should be given promptly to an RhD-negative mother if this has not already been done.
- An ABO antigen determination can show a weakened result.
- A strong prevalence of maternal antibodies on the neonate's RBC may lead to a false negative antigen determination. This must be checked using DAT.
- Serological determination of ABO/RhD in premature infants or neonates who have received intrauterine transfusions may produce false results.

7.3 Testing of children over four months

- The immunohaematological analyses and interpretation of the results are identical to those employed for adults.
- A blood group card can be issued:
  – if a full ABO/RhD antigen determination and reverse typing have been performed
  – and the interpretation of the results conforms with the table in § 5.4.
  – if it is not possible to determine isoagglutinins or perform a full ABO blood group determination, PCR may be used instead (see § 9.8.2 for transfusion)

7.4 Antibody testing in monoclonal antibody therapy

Anti-CD38 (daratumumab or Darzalex) is used to treat multiple myeloma. Anti-CD38 can cause a positive ABS result for up to 6 months after it has been discontinued because RBC also express CD38.

Valid results of an ABS must be available before therapy with monoclonal antibodies such as anti-CD38 begins. It is also recommended to perform extended antigen pheno- or genotyping.

- If a sample is sent to a reference laboratory, the diagnosis and the drug must be stated on the request form.
- If the ABS is negative, by tube method or by using a DTT Panel, pRBC (ABO/RhD/Rh-pheno/K/Kp^{a} compatible) can be released by type & screen.

- Alternatively, antigen- or genotypically compatible pRBC (Rh-pheno, K, Kp^a, Kidd, Duffy, S), without antibody clarification, can be released according to the T&S procedure

8 Selection of blood group for labile blood products

8.1 Selection of ABO/RhD blood group for packed red blood cells

8.1.1 Selection of the ABO blood group

- If possible, the ABO blood group of the pRBC to be transfused must be identical to the patient's blood group.
- Transfusion of products that are not ABO-identical must be avoided unless there is a good medical and/or logistical reason. If an exception is made this needs to be clearly stated.
- If no ABO-identical pRBC are available, or if alloantibodies are present, ABO-compatible products may be transfused.

Table 8.1.1 ABO compatibility rules

Patient's blood group	Blood group of pRBC
O	O
A	A and O
B	B and O
AB	AB, A, B and O

- After non-ABO-identical pRBC have been transfused, the state of medical science and technology requires the products to be switched to the patient's own ABO blood group as soon as this is medically and logistically justifiable. For massive transfusions: see § 9.3.

8.1.2 Selection of the RhD antigen

- For recipients with a normal RhD antigen:
  - The RhD antigen of the selected pRBC should be identical to the RhD antigen of the recipient of the blood.
- If pRBC with identical RhD are not available:
  - RhD-negative pRBC may be given to RhD-positive recipients. However, this must remain the exception. If an exception is made this needs to be clearly stated.
  - In specific exceptional cases, RhD-positive pRBC may be given to RhD-negative recipients (see § 9.3.2).
- For recipients with weak D:
  - Patients with weak D are given RhD-positive pRBC provided that no anti-D has been detected.
  - Girls and women of child-bearing age, i.e. between 0 and 50 years of age (see also § 8.1.3.2), are given RhD-negative pRBC if:
    - the weak D type is not known,
    - they are not weak D type1, 2 or 3.
- For recipients with partial D:
  - Patients with partial D are given RhD-negative pRBC.

Table 8.1.2 Selection of the RhD antigen

	Weak/partial D RhD not investigated by PCR	**Weak D type 1, 2, 3 investigated by PCR**	**Other weak/partial D investigated by PCR**
Transfusions woman < 50	RhD neg.* until the PCR result is available	RhD pos.	RhD neg.*
Transfusions woman ≥ 50	RhD pos.**	RhD pos.	RhD neg.*
Transfusions man	RhD pos.**	RhD pos.	RhD neg.*

* If possible the patient's phenotype Rh/K should be taken into consideration

** If the patient is definitely a partial D, transfuse RhD neg.

8.1.3 Selection of the other blood group antigens

8.1.3.1 Alloantibodies present

If transfusion-relevant alloantibodies are present, the pRBC must be checked for the corresponding antigen(s) and must be negative. This also applies to known clinically relevant antibodies that are no longer detectable.

- Once the first alloantibody has occurred, it is recommended to perform extended antigen typing (Ss, JK, FY, Kk) and to transfuse suitably compatible products whenever possible in order to avoid further immunization. Corresponding genotyping is recommended in patients who have recently received a transfusion. (see § 11).

8.1.3.2 Other indications

- It is recommended to transfuse pRBC with a compatible Rh/K phenotype in the following constellation:
  - For transfusions given to girls and women of child-bearing age (0 to 50 years),
  - Where anti-erythrocyte autoimmunization is present. If the phenotype cannot be determined serologically, Rh/K genotyping must be considered (see § 11).
- This procedure is recommended as a preventive measure. However, patients with irregular antibodies should not be disadvantaged. For this reason, there are limitations in providing c- or e-negative blood for preventive antigen-compatible transfusions.
- Where there is a chronic need for transfusion (e.g. haemoglobinopathies such as sickle cell anaemia, thalassaemia etc.) it is advisable to use pRBC with a compatible Rh/K phenotype and Jk^a, Jk^b, S, s, Fy^a, Fy^b where possible.
- For prophylactic antigen-matched transfusion, it is not necessary to check the stated antigen profile.
- For transfusions in patients who have undergone allogeneic stem cell transplantation, a doctor experienced in transfusion medicine and a specialized laboratory should be involved.

8.2 Selection of ABO blood group for fresh frozen plasma

- If possible, the ABO blood group of the FFP must be identical to the patient's blood group.
- The RhD antigen is not respected for FFP.
- If FFP with an identical ABO is not available, ABO-compatible FFP must be transfused.

Table 8.2 FFP compatibility rules

Patient's blood group	Blood group of FFP
O	O, A, B and AB
A	A and AB
B	B and AB
AB	AB

- Non-ABO-identical FFP transfusions must remain the exception. If an exception is made this needs to be clearly stated.

8.3 Selection of ABO/RhD in platelet concentrates

The following recommendations apply to adults and children:

- The selection of ABO blood group and RhD antigen for PC is determined by the recipient's ABO/RhD blood group and availability.
- When RhD-positive PC are given to RhD-negative patients, consideration should be given to administering Rh prophylaxis as there is a risk of sensitization. This seems to be higher with pooled products than with apheresis products. The indication for Rh prophylaxis must be weighed against the risk of allosensitization on a case-by-case basis.
- Blood group has to be determined only once (in emergency situations PC can also be transfused without determining it).
- When transfusing pathogen-inactivated PC with Intercept, amotosalen based, irradiation for Graft-versus-Host Disease prophylaxis is not necessary (further techniques may be added in the future depending on the approval).

8.4 Selection of ABO/RhD in specific situations

- In case of massive transfusions, autologous transfusions, neonate, intrauterine and exchange transfusions: see § 9.

9 Choice of blood products in specific clinical situations

9.1 Autologous transfusion

To avoid mix-ups, the same pre-transfusion testing should be carried out as for homologous transfusions (see § 4.4 and 4.5 and [22]).

9.2 Emergency transfusion

The chapter describes the situations where there is not enough time to carry out the complete pre-transfusion investigations. The framework conditions and responsibilities for emergency transfusions must have been regulated and documented internally in advance ([22].

In principle, emergency transfusions should also be carried out, if possible with identical blood groups. Whenever possible, a first blood sample should be taken before transfusions/infusions.

9.2.1 Selection of ABO and RhD blood groups for emergency transfusion

- If no blood group is known (without T&S, VP and DAT clarification): EC of blood group O and AB plasma must be administered (see § 9.3 "Massive transfusions")
- If one blood group determination (tube or blood group card) is available: blood group O, RhD EC can be administered identically.
- Two blood group determinations from at least one fresh collection (without AKST) are present: it can be switched immediately to the patient's own blood group if the results are clear (note: the blood group can be difficult to interpret due to mixed fields and dilutions in emergency transfusions).

9.2.2 Other pre-transfusion investigations

- This is immediately followed by an AKST and, if necessary, a DAT on the collected patient blood sample collected before transfusion.
- The doctor responsible for the transfusion must be informed of any previous incompatible transfusions. The doctor in charge decides on any further incompatible transfusions.

9.3 Massive transfusion

9.3.1 General

- Massive transfusion is defined as more than four pRBC (in adults) within one hour, or 50% exchange transfusion within three hours, or full exchange within 24 hours.
- As soon as the massive transfusion protocol is no longer necessary, the normal pre-transfusion test sequence defined in § 4 applies.
- If full pre-transfusion testing could not be carried out (see § 9.2).
- When performing massive transfusions, CT should if possible be carried with a pre-transfusion sample if alloantibodies are present. If there is no pre-transfusion sample, or if the sample has been used up, antigen-negative pRBC with not CT can be released.

9.3.2 Selection of ABO and RhD blood groups for massive transfusions

As soon as the ABO blood group, RhD and results of the ABS are available, the following applies:

- If the ABO group of the transfused pRBC was compatible with but not identical to the patient's ABO blood group, the patient's own blood group can be used at any time. Otherwise section 8.1.1. also applies here analogously.
- When massive transfusions are given, an RhD-positive pRBC may exceptionally be given to an RhD-negative patient (or a patient whose RhD is not known) after the doctor performing the transfusion has been consulted or if doing so is permitted by the hospital's internal directives.
  - This requires that:
    - the required number of units of RhD-negative pRBC are difficult to obtain.
    - no anti-D antibodies have been identified in the patient's serum/ plasma.
    - the patient is a man or a woman who is no longer of child-bearing age.
  - Once the acute bleeding has stopped, the transfusion should be switched to RhD-negative pRBC as soon as possible. Alloimmunization should be excluded every 96 hours if RhD-positive pRBC are continued to be given. An ABS should be performed between 6 and 12 weeks after an incompatible transfusion (see § 6.1).
  - Everything possible must be done to avoid giving RhD-positive pRBC to girls and women who are of child-bearing age (0 to 50 years of age) and who are RhD negative (see also § 8.1.2).

9.4 Autoimmunohaemolytic anaemia

- If patients require a transfusion, a doctor experienced in transfusion medicine and a specialized laboratory should be involved.
- For transfusions in patients with anti-erythrocyte autoantibodies: see § 8.1.3.2

9.5 Chronic transfusion requirement

- For chronic transfusion requirement: see § 8.1.3.2

9.6 Intrauterine transfusions

Immunohaematological testing and the provision of blood for intrauterine transfusions should be performed by a specialized laboratory.

The following rules normally apply to transfusions of pRBC:

- pRBC of blood group O are administered,
- The RhD and Rh/K phenotype must be compatible with the mother's blood. The mother's other antigens should also be taken into account,
- CT-negative pRBC that are compatible with the alloantibodies in the mother's blood must be transfused,
- Concentrated (haematocrit 70–85%) and irradiated pRBC must be used for intrauterine transfusions,
- The storage time should be as short as possible (ideally pRBC should not be more than 5 days old).

9.7 Exchange transfusions

Immunohaematological testing and the provision of blood for exchange transfusions should be performed by a specialized laboratory.

The following rules normally apply to transfusions of pRBC:

- pRBC should be compatible with the ABO blood group of the mother and that of the child,
- CT-negative pRBC that are compatible with the alloantibodies in the mother's blood must be transfused (CT ideally with serum/plasma from the mother, alternatively with serum/plasma from the child).
- Indication for irradiation as well as the age of the pRBC are depended on the child's age and the clinical context. The decision rests with the responsible doctor.

9.8 Transfusions in children

9.8.1 Transfusions in premature infants, neonates and children under four months [13; 14]

The following rules apply:

- pRBC should be compatible with the ABO blood group of the mother and that of the child.
  - Before the first transfusion an AB/D control must be made from a second sample. This ensures a BG and RhD identical transfusion. If not, pRBC of BG O must be administered.
- If the mother has no anti-D, pRBC compatible with the child's RhD are transfused.
- If the mother's ABS and the neonate's DAT are negative, pRBC can be transfused by T&S. In such cases, T&S can be extended to the end of the fourth month of the child's life without the need for further pre-transfusion testing.
- If the mother's ABS and/or the neonate's DAT are positive, the following procedure is adopted after the antibodies have been identified:
  - For the first transfusion, XM is performed with antigen-negative pRBC and serum/ plasma from the mother.
  - If further transfusions are given, XM is done with antigen-negative pRBC and serum/ plasma from the mother as long as the child is < 4 months old. Serum from the mother containing alloantibodies can be frozen and used if needed for testing antigen-negative pRBC.
  - Alternatively, XM can be done with serum/ plasma from the child.
- If the child's positive DAT and/or the mother's positive ABS can be unequivocally attributed to anti-D prophylaxis (passive immunization), no further T&S is required until the child is 4 months old (see bullet point 3). Other maternal alloantibodies must be excluded during differentiation.
- Indication for irradiation as well as the age of the pRBC are dependent on the child's age and the clinical context. The decision rests with the responsible doctor [6; 15].
- The storage time should be as short as possible; ideally the pRBC should not be more than 5 days old. If transfusions products are more than 5 days old, the clinical situation should be discussed with the responsible doctor to avoid complications owing to hyperkalaemia.

- Blood group AB must be selected for transfusions of FFP.

9.8.2 Transfusions in children (4 to 12 months)

The following rules apply:

- Should it be impossible to carry out a full ABO/antigen determination in children over the age of four months because isoagglutinins are not yet present, ABO- and RhD-identical pRBC and BG AB plasma can continue to be transfused. ABO PCR may be considered (see §11).

9.9 Transfusion of irradiated packed red blood cells (see B-CH SRC regulations, chapter 10 "Manufacture", § 10.9.2 "Irradiation of labile blood products")

- pRBC may be irradiated up to a maximum of day 28 after they have been obtained. Irradiated pRBC must be transfused within 14 days and no later than day 28 after withdrawal.
- Patients at risk of hyperkalaemia: irradiated packed red blood cells should be transfused as soon as possible and no longer than 24 hours after irradiation.
- Every hospital should establish a list of indications for irradiated products.

9.10 Procedure for and selection of blood products if allergic/anaphylactic transfusion reactions occur and in IgA-deficient patients

The association between IgA deficiency (<70 mg/dl (0.7g/l)) or selective IgA deficiency (lack of IgA, < 0.05 mg/dl) in patients (with and without the presence of anti-IgA antibodies) and allergic / anaphylactic transfusion reactions is a controversial topic in the literature [16;17]. In a Swiss study of 15'000 blood donors, a selective IgA deficiency was identified with a frequency of about 1:850 [18].

Following a transfusion-associated severe allergic/anaphylactic reaction, clarification of a possible IgA deficiency is recommended.
Caution: the blood sample should be taken prior to transfusion (plasma/pRBC) and the administration of immunoglobulin.

The IgA concentration of pRBC and PC products (and the concentration of all other plasma components) can be minimized by "washing". When IgA deficiency and severe allergic transfusion reactions are combined, the administration of washed pRBC and PC or plasma from IgA deficient donors can be considered as a precautionary measure. In exceptional cases, the latter can be used for transfusions that can be planned well in advance.

Please contact your blood transfusion service for acquisition of all these special products.

10 Adverse transfusion reactions

This document mentions only those adverse transfusion reactions that occur in the context of pre-transfusion testing of patients' samples.

10.1 General

Adverse transfusion reactions and transfusion-related incidents must be investigated in accordance with the applicable legal requirements for haemovigilance [1].

- The doctor performing the transfusion must take the various causes of transfusion reactions into account and initiate steps to investigate them.
- Adverse transfusion reactions must be reported immediately to the laboratory that performed the pre-transfusion testing so that the circumstances can be investigated without delay.
- Blood products that have led to adverse transfusion reactions, and all other blood products that could be affected, must be withdrawn from circulation immediately.
- If the quality of the blood products is suspected of being responsible for the adverse transfusion reactions, the manufacturer must be informed immediately so that all other potentially affected products (e.g. from the same donor) can be blocked or recalled.

10.2 Investigation of suspected haemolytic transfusion reactions

10.2.1 Materials

- The following materials are required to investigate a possible haemolytic transfusion reaction:
  - Pre-transfusion blood samples from the recipient,
  - Segments and/or blood bags from all blood products that have recently been transfused,
  - A sample taken from the recipient immediately after the transfusion reaction occurred.

10.2.2 Immunohaematological investigation

- Possible administrative errors and mix-ups must be investigated.
- The following investigations of samples of the patient's blood obtained pre- and post-transfusion must be performed:
  - Visual inspection of the patient's plasma/serum for haemolysis before and after transfusion
  - Full determination of ABO/RhD using blood samples obtained from the patient pre- and post-transfusion,
  - An ABS with blood samples obtained from the patient pre- and post-transfusion,
  - DAT . If the DAT is positive, elution of the post-transfusion blood sample is performed.
  - If the DAT is negative but there are signs of haemolysis, elution must still be performed,
  - XM of samples obtained from the patient pre- and post-transfusion with all transfused pRBC.
- Investigation of all transfused blood products:
  - Visual inspection (colour and homogeneity),
  - AB/RhD antigen check of the segments of the pRBC and, where indicated, Rh/K phenotype and other blood group antigens,
  - For FFP and PC, reverse typing is performed using the blood bags.

10.2.3 Further investigations

- If an adverse transfusion reaction occurs, it is the responsibility of the doctor performing the transfusion to arrange further investigations.

10.3 Reporting

Adverse transfusion reactions are reported either directly to Swissmedic by the haemovigilance officer or by the doctor who performed the transfusion using the haemovigilance form and, if the quality of the blood products might have been the cause, to the manufacturer.

11 Standards for molecular blood group typing

The new chapter 11 is divided into the following sections:

A: Applications

C: EPT and Quality Control

L: Nucleic Acid Analysis

P: Processing

R: Reporting

Z: Appendix

Sections A: Applications, P: Processing, R: Reporting and Z: Appendix were authored independently by a subgroup of the immunohaematology working group.

Sections C: EPT and Quality Control and L: Nucleic Acid Analysis were adopted word-for-word from sections C and L of version 6.3 of the Standards for Histocompatibility and Immunogenetics Testing (HLA) published by the European Federation for Immunogenetics (EFI).

The original EFI standards were shortened by omitting certain subsections. The remaining sections and subsections are identical word-for-word to the EFI standards and should remain so (direct adoption of future EFI standards).

EFI has consented to the use of its sections C and L for chapter 11 “Standards for Molecular Blood Group Typing”.

1.1 Other sections of this document in which molecular blood group typing is mentioned:

1	**2.2.2**	**External quality controls**
2	**5.1**	**Definitions – general**
3	**5.3**	**Molecular genetic methods**
4	**5.4.3**	**Determination of the RhD antigen**
5	**5.4.4**	**Determination of the Rh/K phenotype and the other blood group antigens**
6	**5.4.5**	**Anomalous/non-interpretable results**
7	**7.2.1**	**Table 7.2.1 Anti-D prophylaxis and PCR**
8	**8.1.2**	**Table 8.1.2 Selection of the RhD antigen**
9	**8.1.3.1**	**Selection of the other blood group antigens**
10	**8.1.3.2**	**Other indications (anti-erythrocyte autoimmunization)**

A. Applications of Molecular Blood Group Detection

	* donor genotyping is not topic of this recommendation	comments and examples	reci-pients	do-nors*
A 1	**Clarification of serological prevalues**			
A 1 1	ABO antigen and isoagglutinine discrepancies		+	+
A 1 2	*RHD* categories and partials		+	+
A 1 3	antigens reacting discrepant with different moAB (all blood groups)		+	+
A 2	**Presence of antibodies (all blood groups)**			
A 2 1	Presence of allo-antibody		+	+
A 2 2	Presence of auto-antibody		+	+
A 3	**Determination of weakly agglutinating antigens**			
A 3 1	Determination of weak D type 1, 2 & 3.	recommended for girls and women of child-bearing age (for premenopausal females)	+	+
A 3 2	Determination of weak D type others than 1, 2 & 3.		+	+
A 3 3	Determination of antigens with weak agglutination of all blood groups		+	+
A 4	**Determination of antigens only detectable by adsorption/elution**			
A 4 1	Detection of RhDs only detectable by adsorption/elution ("Del")	also in screening for *RHD* in RhD negatives	-	+
A 4 2	Detection of antigens only detectable by adsorption/elution of all blood groups		+	+
A 5	**Clarification of geno-/phenotype discrepancies**		+	+
A 5 1	Case phenotype correct positive, genotype false negative	e.g. alleles with "primer-binding-site" mutations.	+	+
A 5 2	Case phenotype correct negative, genotype false positive	"null-alleles", recognized by carrying an "N" in ISBT term.	+	+
A 5 3	Case phenotype false positive, genotype correct negative	*RHD*01N.06* (DCeS) with pseudo RhC, though genetically RHC negative. St(a) / GYP*401 alleles of MNSs.	+	+
A 5 4	Case phenotype false negative, genotype correct positive	e.g. Del vs. *RHD*01EL.01*	+	+
A 6	**Screening for *RHD* among RhD negatives**			
A 6 1	Detection of RhD negative *RHD-CE-D* hybrid alleles		-	+
A 6 2	Detection of unexpressed (RhD negative) RHD genes		-	+

A 7		**Detection of blood groups in case no commercial reagents for serological detection are available**			
A 7	1	Detection of Dombrock blood group system	Do(a/b), Au(a/b),…	+	+
A 7	2	Rare blood group antigens / high frequency antigen (HFA) negatives	Di(a/b), Sc1/Sc2,…	+	+
A 7	3	Rare blood group antigens of defined ethnicities	e.g. Rh, VS, V, hr^b, … In(a/b),	+	+
A 8		**Prenatal**			
A 8	1	Prenatal detection of blood groups from fetal material		+	-
A 9		**Blood group assessment in special clinical situations**			
A 9	1	Mol. BG determination in polytransfused patients		+	-
A 9	2	Mol. BG determination in DAT positive individuals		+	-
A 9	3	Monoclonal Hematopoiesis (loss of BG allels)		+	-
A 9	4	Post stem cell transplantation		+	-
A 9	5	Chronic transfusion needs (Thalassemia, Sickle Cell Disease, MDS, etc.)		+	-
A 10		**Use of alternative sample material**			
A 10	1	If indicated, alternative sample material may be used		+	-

C. External Proficiency Testing - Qualification

according to:

European Federation for Immunogenetics (EFI)

STANDARDS FOR HISTOCOMPATIBILITY & IMMUNOGENETICS TESTING
version 6.3

Accepted by the Standards and Quality Assurance Committee on 26th April 2015
Accepted by the EFI Executive Committee on 16th July 2015

Effective from October 1st 2015

comment-1: [ ] … rectangular brackets indicate changes with respect to the EFI standards, e.g. [BG vs. ~~HLA~~] in these "Standards for Molecular Blood Group Typing"

C 6	**External Proficiency Testing (EPT)**	
C 6 1	The laboratory must participate in EPT programme(s) to cover	
C 6 1 1	All the accredited laboratory applications [of Molecular Blood Group Typing as exemplified by e.g. Instand e.V., or UK Neqas ~~HLA typing, antibody screening and identification, crossmatching, etc.~~]	[BG vs. HLA]
C 6 2	Procedure of EPT	
C 6 2 1	The procedure for testing EPT samples including the allocation to techniques must be documented prior to the annual commencement of the EPT cycle	
C 6 3	EPT samples must be	
C 6 3 1	Tested by the same techniques as routinely employed for clinical samples, either individually or in combination	
C 6 3 2	Interpreted in a manner comparable to routine clinical samples	
C 6 3 3	Incorporated into the laboratory's routine workload	
C 6 4	Minimum number of samples for EPT per year	
C 6 4 1	Blood Group Genotyping	
C 6 4 2	[2 times per year, 4 samples each, specificities as currently requested by Instand e.V., or UK Neqas]	[BG vs. HLA]
C 6 5	Reporting of EPT results	
C 6 5 1	Participants must report:	
C 6 5 1 1	The antigen specificities and alleles identified	
C 6 5 1 2	The method(s) used	
C 6 6	Laboratory performance	
C 6 6 4	Participating laboratories must ensure that all the following EPT related documents are maintained and are made available to [~~EFI~~] inspectors [of the Swiss Accreditation Service (SAS)] for assessment:	[BG vs. HLA]
C 6 6 4 1	Submitted worksheets	
C 6 6 4 2	EPT summary/scheme reports	
C 6 6 4 3	Annual performance	
C 6 6 4 4	Participation certificates	
C 7	**Competency Evaluation and Continuous Education**	
C 7 2	The Laboratory Director and the technical staff must participate in continuing education relating to each category [~~for which~~ of Molecular Blood Group Typing (e.g. single sample typing, blood group sequencing,…) ~~HLA EFI accreditation is sought~~].	[BG vs. HLA]

L. Nucleic Acid Analysis

according to:

European Federation for Immunogenetics (EFI)

STANDARDS FOR HISTOCOMPATIBILITY & IMMUNOGENETICS TESTING
version 6.3

Accepted by the Standards and Quality Assurance Committee on 26th April 2015
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Effective from October 1st 2015

comment-1: [ ] … rectangular brackets indicate changes with respect to the EFI standards, e.g. [BG vs. ~~HLA~~] in these "Standards for Molecular Blood Group Typing"	[BG vs. HLA]	comment added
comment-2: most current versions of the ISBT Blood Group Allele Tables (plus actual version number) are given at: http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/	[BG vs. HLA]	comment added

L 1	**General laboratory design**
L 1 1	Laboratories performing amplification of nucleic acids must use:
L 1 1 1	A dedicated work area with restricted traffic flow
L 1 1 2	Physical barriers to prevent DNA contamination, including the use of dedicated:
L 1 1 2 1	Equipment
L 1 1 2 2	Laboratory coats
L 1 1 2 3	Disposable supplies
L 1 2	Pre-amplification procedures must be performed in an area which excludes amplified DNA that has the potential to serve as a template for amplification in any of the genetic systems tested in the laboratory
L 1 3	All activities occurring from and including thermal cycling must take place in the post-amplification area
L 2	**Equipment**
L 2 1	Accuracy of thermal cycling instruments:
L 2 1 1	Must be verified by maintenance according to the manufacturer, or
L 2 1 2	Must be verified by annual thermal verification of the block using a calibrated device designed specifically for this purpose
L 3	**Reagents**
L 3 3	The appropriate performance of individual products must be documented before results using these reagents are reported for:
L 3 3 1	Each shipment, and
L 3 3 2	Each lot
L 3 4	For commercial kits, the following information must be documented:
L 3 4 1	Source
L 3 4 2	Lot number
L 3 4 3	Expiry date
L 3 4 4	Storage conditions

L 3 5	Reagents from different lots of commercial kits must not be mixed, unless either:		
L 3 5 1	Specified by the manufacturer, or		
L 3 5 2	Validated and documented with appropriate quality control in the laboratory		
L 4	**Primers**		
L 4 1	The specificity of primer combinations and the annealing positions must be defined		
L 4 2	Laboratories must:		
L 4 2 1	Have a policy for quality control of each lot or shipment of primers		
L 4 2 2	Confirm the specificity and quantity of the amplified product using reference material		
L 4 2 3	Test each lot and shipment of commercial kits against at least one DNA sample of known type		
L 5	**Nucleic acid extraction**		
L 5 1	The method used for nucleic acid extraction:		
L 5 1 1	Must be published and documented		
L 5 1 2	Must be validated in the laboratory		
L 5 2	Purity and concentration of Nucleic Acids:		
L 5 2 1	Must be sufficient to ensure reliable test results		
L 5 2 2	Should be determined for each sample, or		
L 5 2 3	If not determined for each sample, the laboratory must have tested and validated this policy		
L 5 3	If the DNA is not used immediately after purification, suitable methods of storage must be available that will protect the integrity of the material		
L 6	**Electrophoresis**		
L 6 1	[~~Optimal~~] Electrophoretic conditions must be documented	[BG vs. HLA]	"optimal" deleted from Standards for Molecular Blood Group Typing
L 6 2	The laboratory must establish criteria for accepting each slab or capillary gel migration, and each lane of a gel or capillary injection		
L 6 2	When the size of an amplicon is a critical factor in the analysis of data, size markers that produce discrete electrophoretic bands spanning and flanking the entire range of expected fragment sizes must be included in each gel		
L 7	**Analysis**		
L 7 2	The method of allele assignment must be designated		
L 7 3	The [ISBT Blood Group Allele Tables ~~IMGT/HLA database~~] must be:	[BG vs. HLA]	changed IMGT/HLA to ISBT
L 7 3 1	Documented		
L 7 3 2	Updated at least once a year with the most current version of the [ISBT Blood Group Allele Tables ~~IMGT/HLA database~~]	[BG vs. HLA]	changed IMGT/HLA to ISBT
L 7 4	If a manual allele call or interpretation of positive/negative reactions is performed for SSOP or SSP, two independent interpretations of primary data must be performed, except under justified special emergency situations		

L 8	**If there is evidence (suspect) for contamination**		
L 8 3	If amplified product is detected, there must be:		
L 8 3 1	Written description of how to eliminate the contamination		
L 8 3 2	Measures taken to prevent future contamination		
L 8 3 3	Evidence of elimination of the contamination		
L 9	**Typing using sequence-specific primers (SSP)**		
L 9	**comment-5:** in house developed tests are addressed, versus for commercial products, responsibility for correct allele-detection lies within the manufacturers.	[BG vs. HLA]	comment added
L 9 1	Each amplification reaction must include controls to detect technical failures (e.g. an internal control such as additional primers or templates that produce a product that can be distinguished from the typing product)		
L 9 3	The laboratory must use the following data in the interpretation phase of the typing:		
L 9 3 1	Information derived from the validation process		
L 9 3 2	Information derived from previous typings with the same lot of primers		
L 10	**Sequence-Based typing (SBT)**		
L 10 1	Sequencing Templates:		
L 10 1 1	Must have sufficient purity, specificity, quantity and quality to provide interpretable sequencing data		
L 10 1 2	Should be purified after amplification to eliminate the presence of dNTPs, Taq polymerase and amplification primers		
L 10 1 7 2	For each run the size of fragments must be documented and the selection must be specified		
L 10 2	Sequencing Reaction		
L 10 2 1	The specificity of the template in combination with the sequencing primer ([ISBT Blood Group Allele locus (gene) and alleles ~~HLA locus and alleles~~)] must be defined.	[BG vs. HLA]	changed IMGT/HLA to ISBT
L 10 2 2	Quantity and quality of templates, sequencing primers and sequencing reagents must be sufficient to provide interpretable primary sequencing data		
L 10 2 3	The conditions for the sequencing reaction must be documented and appropriate for obtaining reliable primary sequencing data.		
L 10 3	Nucleotide Assignment		
L 10 3 2	The signal to noise ratio must be sufficient to ensure reliable nucleotide assignments		
L 10 4	Allele assignment	[BG vs. HLA]	overlap with reporting
L 10 4 2	Criteria for allele assignment must be established	[BG vs. HLA]	overlap with reporting (go to NCBI BLAST plus check ISBT allele tables)
L 12	**Other Methods**		
L 12 1	If alternative methods (e.g. SSCP, heteroduplex, DGGE) are used for [Molecular Blood Group ~~HLA~~] typing, there must be established procedures in place which	[BG vs. HLA]	changed IMGT/HLA to ISBT

L 12 1 1	Must be validated
L 12 1 2	Must include sufficient controls to ensure accurate assignment of types for every sample
L 12 1 3	Must comply with all relevant standards from section L **(Nucleic Acid Analysis)**
P	**P. Processing of molecular data**
	comment-1: most current versions of the ISBT Blood Group Allele Tables (plus actual version number) are given at: http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/
P 1	Molecular Blood Group Typing may start from any appropriate source of molecular raw data, e.g. SNP typing, sequencing and others done on resources such as RNA and DNA.
P 2	Raw molecular data, must be translated to "haplotype alleles", commonly described by the term "alleles" within this document.
P 2 1	Current versions of the allele names as proposed by the ISBT terminology committee must be used, whenever available.
P 2 2	In case of the discovery of new alleles and description of blood group alleles with non-existent ISBT names, <Trivial Names> for alleles must be used.
P 2 2 1	Naming of new alleles with Trivial Names should be done in a way to avoid confounding with existent (and potential future) ISBT allele names.
P 2 2 2	There should be written records for each newly discovered allele (with a Trivial Name).
P 2 2 3	Newly discovered alleles should be reported in peer reviewed journals, the obtained sequences submitted to nucleotide databases and the discovery be reported to the respective point-persons of the ISBT terminology committee.
P 3	The two parental alleles must be described as a <Genotype>.
P 3 1	Homozygosity may best be described by naming the respective allele only.
P 3 2	Homozygosity for *RHD* (and similar genes) may best be inferred by Rhesus box analysis or quantitative methods.
P 3 3	Proven homozygosity for *RHD* (and similar genes) may be declared naming the respective *RHD* alleles twice.
P 3 4	Untested zygosity determination for *RHD* (and similar genes) may be indicated similarly to serology by a dot <RHD /" " >.
P 3 5	If indicated, a third allele name per gene locus may be given in case of duplicated genes on one haplotype (e.g. *GYP*401*)
P 5	There should be written records for each genotype assignment to the Predicted Blood Group Phenotype ("interpretation matrices"), also considering newly discovered alleles (with Trivial Names).
	R. External Reporting of Results
R 1	Methods used, e.g. SNP typing, sequencing, and others, and type of material investigated (RNA, DNA), must be declared.
R 1 2	When reporting SNP results, genetic positions of polymorphisms tested must be indicated as given by the ISBT terminology.
R 2	Current versions of the allele names as proposed by the ISBT terminology committee must be used, whenever available.
R 3	In case of the discovery of new alleles and description of blood group alleles with non-existent ISBT names, <Trivial Names> for alleles must be used.

R 4 The two parental alleles must be described as a <Genotype>.

R 5 Every genotype must be translated into a <Predicted Blood Group Phenotype>.

R 6 All above mentioned documentations may be commented, especially for rare allele**s** and uncommon genotype occurrences.

R 7 There should be a transfusion recommendation, especially for rare alleles, uncommon genotype occurrences and newly discovered alleles (with Trivial Names).

Z. Commonly known BG polymorphism

Z 1 APPENDIX 1: commonly recognized alleles with known BG phenotypes

Appendix Z: Commonly known BG polymorphism with known effects on BG phenotypes

Blood Group System	ISBT #	Blood Group	Gene (HGNC)	on	Chromo-some	allele name 1	allele name 2	nt position	nt 1	nt 2	amino a.	anti-gens	allele ct.	SNP ct.	rs #
ABO	001	ABO A vs O1	*ABO*	9q	9q34.2	*ABO*wt*	*ABO*O.01*	261	G	del G	fsThr88Pro	1	2	1	rs8176719
ABO	001	ABO A vs O2	*ABO*	9q	9q34.2	*ABO*wt*	*ABO*O.02*	802	G	A	Gly268Arg	-	1	1	rs41302905
ABO	001	ABO A vs B	*ABO*	9q	9q34.2	*ABO*wt*	*ABO*O.02*	803	G	C	Gly268Ala	1	1	1	rs8176747
MN	002	M / N	*GYPA*	4q	4q31.21	*GYPA*01*	*GYPA*02*	59	C	T	Ser20Leu	2	2	1	rs7682260
Ss	002	S / s	*GYPB*	4q	4q31.21	*GYPB*03*	*GYPB*04 (wt)*	143	C	T	Thr48Met	2	2	1	rs7683365
RhD	004	RhD+ / RhD-	*RHD / RHCE*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01N.01*	455	A	[C]	Asn152[Thr]	2	2	1	rs17418085
RhD	004	RhD+ / RhD-	*RHD / RHCE*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01N.01*	787	G	[A]	Gly263[Arg]	-	-	1	rs3118454
RhD	004	RhD+ / RhD-	*RHD / RHCE*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01N.01*	1362	A	[T]	-	-	-	1	no rs
RhD	004	RhD+ / RhD-	*RHD / RHCE*	1p	1p36.11	*RHD*01 (wt)*	*RHD*04N.01*	504-541	-	ins 37 bp	-	-	1	1	no rs
RhD	004	RhD+ / RhD-	*RHD / RHCE*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01N.06*	1006	G	C	Gly336Gly	-	1	1	no rs
RhD	004	RhD+ / RhD partial	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*05.01, or RHD*DV.1*	667	T	G	Phe223Val	-	-	-	rs1053356
.	.	.	.	.	.	.	.	697	G	C	Glu233Gln	-	-	-	rs1053359
RhD	004	RhD+ / RhD partial	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*05.07, or RHD*DV.7*	667 ... to	T	G	Phe223Val	-	-	-	rs1053356
RhD	004	RhD+ / RhD partial	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*06.01, or RHD*DVI.1*	505 ... to	A	C	Met169Leu	-	-	-	rs17421137
RhD	004	RhD+ / RhD partial	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*07.01, or RHD*DVII.1*	329	T	C	Leu110Pro	-	-	-	rs121912762
RhD	004	RhD+ / RhD weak	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01W.1, or RHD*weak D type 1*	809	T	G	Val270Gly	-	-	-	rs121912763
RhD	004	RhD+ / RhD weak	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01W.2, or RHD*weak D type 2*	1154	G	C	Gly385Ala	-	-	-	rs71652374
RhD	004	RhD+ / RhD weak	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01W.3, or RHD*weak D type 3*	8	C	G	Ser3Cys	-	-	-	rs144969459
RhD	004	RhD+ / RhD Del	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01EL.01, or RHD*DEL1*	1227	G	A	Lys409Lys	-	-	-	rs549616139
RhD	004	RhD+ / RhD Del	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*01EL.08, or RHD*DEL8*	486+1 = IVS3+1g>a	g	a	splice mutant	-	-	-	rs371990272
RhD	004	RhD+ / RhD weak, partial, Del	*RHD*	1p	1p36.11	*RHD*01 (wt)*	*RHD*11, or RHD*weak partial 11*	885	G	T	Met295Ile	-	-	-	rs371803235
RhCE	004	Rhc / RhC	*RHCE*	1p	1p36.11	*RHCE*01 (03) (wt)*	*RHCE*02 (04)*	i2+3095	-	ins 109 bp	-	2	2	1	no rs
RhCE	004	Rhc / RhC	*RHCE*	1p	1p36.11	*RHCE*01 (03) (wt)*	*RHCE*02 (04)*	307	C	T	Ser103Pro	-	-	1	rs676785
RhCE	004	RhC, Rhc / RhC^w	*RHCE*	1p	1p36.11	*RHCE*all*	*RHCE*02.08*	122	A	G	Gln41Arg	1	1	1	rs138268848
RhCE	004	Rhe / RhE	*RHCE*	1p	1p36.11	*RHCE*01 (02)*	*RHCE*03 (04)*	676	G	C	Pro226Ala	2	2	1	rs609320
Lutheran	005	Lu^a / Lu^b	*BCAM*	19q	19q13.32	*LU*01*	*LU*02 (wt)*	230	A	G	His77Arg	2	2	1	rs28399653
Kell	006	K / k	*KEL*	7q	7q34	*KEL*01*	*KEL*02 (wt)*	578	T	C	Met193Thr	2	2	1	rs8176058
Kell	006	Kp^a / Kp^b	*KEL*	7q	7q34	*KEL*02.03*	*KEL*02 (wt)*	841	T	C	Trp281Arg	2	1	1	rs8176059
Kell	006	Js^a / Js^b	*KEL*	7q	7q34	*KEL*02.06*	*KEL*02 (wt)*	1790	C	T	Pro597Leu	2	1	1	rs8176038
Duffy	008	Fy^a /Fy^b	*DARC*	1q	1q23.2	*FY*01, or FY*A*	*FY*02, or FY*B*	125	G	A	Gly42Asp	2	2	1	rs12075
Duffy	008	Fy^b / Fy^x	*DARC*	1q	1q23.2	*FY*02*	*FY*02M*	265	C	T	Arg89Cys	-	1	1	rs34599082
Duffy	008	$Fy^{a,b}$ / Fy null	*DARC*	1q	1q23.2	*FY*02*	*FY*02N.01*	P-67t>c	T	C	-	1	1	1	rs2814778
Kidd	009	Jk^a /Jk^b	*SLC14A1*	18q	18q11-q12	*JK*01, or JK*A*	*JK*02, or JK*B*	838	G	A	Asp280Asn	2	2	1	rs1058396
Diego	010	Di^a / Di^b	*SLC4A1*	17q	17q21.31	*DI*01*	*DI*02 (wt)*	2561	T	C	Leu854Pro	2	2	1	rs2285644
Wright	010	Wr^a / Wr^b	*SLC4A1*	17q	17q21.31	*DI*02.03*	*DI*02 (wt)*	1972	A	G	Glu658Lys	2	2	1	rs75731670
Cartwright	011	Yt^a / Yt^b	*ACHE*	7q	7q22.1	*YT*01 (wt)*	*YT*02*	1057	C	A	His353Asn	2	2	1	rs1799805
Scianna	013	SC:1, SC:2	*ERMAP*	1p	1p34.2	*SC*01 (wt)*	*SC*02*	169	G	A	Gly57Arg	2	2	1	rs56025238
Dombrock	014	Do^a / Do^b	*ART4*	12p	12p12.3	*DO*01*	*DO*02 (wt)*	793	A	G	Asn265Asp	2	2	1	rs11276
Colton	015	Co^a / Co^b	*AQP1*	7p	7p14.3	*CO*01.01 (wt)*	*CO*02*	134	C	T	Ala45Val	2	2	1	rs28362692
Landsteiner-Wiener	016	LW^a / LW^b	*ICAM-4*	19p	19p13.2	*LW*05 (wt)*	*LW*07*	299	A	G	Gln100Arg	2	2	1	rs77493670
Indian	023	In^a / In^b	*CD44*	11p	11p13	*IN*01*	*IN*02 (wt)*	137	G	C	Arg46Pro	2	2	1	rs121909545
Vel	n.a.	Vel+ / Vel-	*SMIM1*	1p	1p36.32	*[SMIM1*Vel+]*	*[SMIM1*Vel-]*	64-80	-	del 17 bp	-	1	2	1	rs566629828
[Hum. Platelet AG 1]	n.a.	[HPA-1a / b]	*ITGB3*	17q	17q21.32	*[ITGB3*001] (HPA-1a) (wt)*	*[ITGB3*002] (HPA-1b)*	176	T	C	Leu59Pro	2	2	1	rs5918
[Hum. Platelet AG 5]	n.a.	[HPA-5a / b]	*ITGA2*	5q	5q11.2	*[ITGA2*001] (HPA-5a) (wt)*	*[ITGA2*002] (HPA-5b)*	1600	G	A	Glu534Lys	2	2	1	rs10471371

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