Vox Sanguinis International forum on the selection and preparation of blood components for intrauterine transfusion

Clarke, G.; Bodnar, M.; Lozano, M.; Nadarajan, V.S.; Lee, C.; Baud, D.; ... ; Lieberman, L.

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INTERNATIONAL FORUM

Vox Sanguinis International forum on the selection and preparation of blood components for intrauterine transfusion: Responses

Gwen Clarke, Melanie Bodnar, Miquel Lozano, Veera Sekaran Nadarajan, Christina Lee, David Baud, Giorgia Canellini, Tobias Gleich-Nagel, Oscar Walter Torres, Patricia L. Rey, Carolina Bonet Bub, José Mauro Kutner, Lilian Castilho, Nabiha H. Saifee, Meghan Delaney, Theresa Nester, Agneta Wikman, Eleonor Tiblad, Luca Pierelli, Antonella Matteocci, Maddalena Maresca, Emeline Maisonneuve, Anne Cortey, Jean-Marie Jouannic, Jordi Fornells, Arjan Albersen, Masja de Haas, Dick Oepkes & Lani Lieberman

Veera Sekaran Nadarajan & Christina Lee

Malaysia

Indication for IUT

Question 1

The indication for IUT in our institution has to date been limited to red cell alloimmunization due to anti-D. Alpha thalassaemia and congenital infections such as Parvovirus are not uncommon in this region of the world, but the foetal and neonatal specialists in our centre have generally not advocated IUT for them. Certainly, we would not embark on an IUT programme for HbBarts that would be considered as incompatible with life.

Question 2

Anti-D has been the only reason for IUT in our population. We identify anti-D in 0·35% of our non-transfused female population, mainly from the antenatal clinic. The majority of this is due to anti-D administered through the antenatal anti-D prophylaxis programme, but we do get 1–2 cases that occur as a result of RhD immunization resulting in moderate to severe HDFN.

The common antibodies we otherwise identify in our non-transfused female population (prevalence in parentheses) are anti-Mi^{a} (0·24%), anti-Le^{a} (0·24%), anti-E (0·14%) and anti-M (0·12%). As you would note, these antibodies are rarely associated with HDFN. Anti-K and anti-c which are more commonly associated with HDFN has a prevalence of only 0·01% in our population of non-transfused females.

Question 3

We only perform 1–2 IUTs per year. In 2018, we had no IUT procedures and in 2019, we have only performed one procedure to date.

Blood sample testing

Question 4

Foetal red cell typing is limited to ABO and RhD, C, c, E and e phenotyping.

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

We select Group O red cells, preferably from a donor with low titres of anti-A/B. If a suitable donor with low anti-A/B titre cannot be located, we will elect to reconstitute the red cells with AB plasma.

Question 6

We obtain allogeneic red cells from our pool of selected donors.

Question 7

All red cell units supplied are K negative as well as antigen matched as close as possible to the maternal phenotype. At the minimum, the red cells supplied must be CcEe-matched.

Question 8

Units supplied would be considered Day-0, as we prepare red cells from a fresh bleed on the day of the IUT procedure. The donor workup which includes ABO and RhD typing, red cell phenotyping, antibody screening, IAT crossmatch with maternal plasma, anti-A/B titration as well as microbiology testing (HIV, HBV, HCV, TPPA, NAT) would be completed prior to the donation from a sample obtained from the donor not more than 72 h before the planned blood collection.

Question 9

Whole blood is collected into a collection bag containing CPD (Citrate, Phosphate and Dextrose) prior to processing.

Question 10

No, we do not assess CMV status. CMV prevalence is high within our population, and we therefore have found it difficult to maintain a pool of suitable CMV donors.

Question 11

We perform leukoreduction as an alternative to CMV testing.

Question 12

No, sickle status is not tested as the prevalence of the mutation is extremely low in our population.

Question 13

We perform an iso-haemagglutin in titre screen. If the iso-haemagglutin in titre is less than1:50, we do not reconstitute the O blood unit with AB plasma.

Blood product preparation

Question 14

We are a university-based blood transfusion department that handles blood collection, testing, processing and clinical supply to hospital patients. Therefore, the entire process including preparation for IUT is handled by us. In other centres, the blood supplier is tasked with the preparation.

Question 15

Red cell units are reconstituted with AB plasma only if the anti-A/B iso-haemagglutinin titres are high.

Question 16

Manual centrifuging

Question 17

75–85%

Question 18

Yes. Irradiation at 25Gy is performed on a gamma irradiator which is available on-site.

Question 19

The selected donor should be a non-transfused regular male donor who meets all standard donor acceptance criteria.

Blood product administration

Question 20

The amount of blood to be transfused is determined by the perinatologist based on a formula as available on Perinatology.com (http://perinatology.com/protocols/rhc.htm)

Question 21

We release the blood unit at ambient temperature (22 ± 2°C), without any refrigeration as the blood is donated and processed on the same morning of the day of procedure.

Transfusion monitoring and traceability

Question 22

No, we have not had adverse transfusion reactions in the foetus in any of our procedures. However, in the last IUT performed, the mother complained of uterine contractions post-IUT that was stabilized with tocolytics.

Question 23

Records of the IUT are documented in the mother's patient record. However, there is no automatic linking of the IUT to the neonate's clinical or transfusion record after birth. Linking of the IUT to the neonatal record is done manually.

Veera Sekaran Nadarajan
University Malaya Medical Centre
Jalan Universiti, Lembah Pantai
50603 Kuala Lumpur
Federal Territory of Kuala Lumpur, Malaysia
Telephone: +60379492916
Email: veera@ummc.edu.my

Christina Lee
University Malaya Medical Centre
Jalan Universiti, Lembah Pantai
50603 Kuala Lumpur
Federal Territory of Kuala Lumpur, Malaysia
Telephone: +60163209179
Email: christina.lee@ummc.edu.my

David Baud, Giorgia Canellini & Tobias Gleich-Nagel

Switzerland

Indication for IUT

Question 1

IUT is performed based on the following indications:
- Red cell alloimmunization
- Foetal anaemia due to parvovirus
- Feto-maternal haemorrhage
- Twin-To-Twin Transfusion Syndrome
- Alpha thalassaemia
- Platelet transfusion
- Twin anaemia polycythaemia sequence (TAPS)

Question 2

At our institute, alloimmunization during pregnancy leading to an IUT is mostly caused by anti-D. This is in line with the current literature, highlighting the importance of anti-D alloimmunization during pregnancy despite the successful RhD prophylaxis in women [1]. However, in 2018, we had one case of severe anti-Vw mediated HDFN with the necessity of a subsequent IUT. In the Caucasian population, the frequency of antigen Vw is very low with an incidence of 0·06%. Interestingly, in southeast Switzerland an increased allele frequency (1·4%) can be observed. We have had no cases of foetal anaemia requiring IUT with the other antibodies known to be dangerous such as anti-K and anti-c.

Question 3

In 2018, nine IUTs were performed in a total of six patients. Three patients, one alloimunization with anti-D, one with anti-Vw and one infection with a parvovirus, needed one IUT during pregnancy. In another case, a twin pregnancy was marked by anaemia of one of the foetuses and consequently an IUT was required. Two more patients needed two and three IUTs respectively. Both were heavily immunized with an anti-D antibody.

Blood sample testing

Question 4

If a foetal blood sample is transferred to our laboratory, the ABO group as well as the Rhesus (Cc D Ee) and Kell phenotype are determined. A polyspecific direct antiglobulin test (DAT) is systematically performed on all foetal blood samples. A positive polyspecific DAT will be followed up by a monospecific DAT (IgG, C3d, IgM, IgA). If the monospecific DAT is positive, elution analysis are carried out and IgG subclasses are determined.

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

In our department, RBC units of the group 0 Rhesus negative or positive are selected for IUT. Additionally, they are matched with the mother's antibodies and extended phenotype. However, we do not use plasma for IUT.

Question 6

The RBC units chosen for IUT are of allogeneic origin. In rare cases such as a complex immunisation or an immunisation against a high frequency antigen, RBC units for IUT could be collected from the mother.

Question 7

If RBC units are selected for an IUT, these units are routinely matched with the extended phenotype of the mother. This includes the systems Rhesus (CcEe), Kell (K), Duffy (Fy^a, Fy^b), Kidd (Jk^a, Jk^b) and MNS (S, s). Extended phenotype matching should prevent any further immunisation since it is well established that mothers receiving an IUT are at high risk to form an additional antibody either against antigens found on the donor cells or on foetal RBCs [2].

Question 8

The age of RBC units selected for IUT is $\leq$5 days in order to reduce the risk of hyperkalemia in the foetus.

Question 9

Red blood cell units are resuspended in SAG-M additive solution after the collection and separation process.

Question 10

Blood donors are not routinely screened for their CMV status at the Interregional Blood Transfusion SRC. Consequently, CMV status of RBC units designated for IUT has to be performed on request before transfusion. Only CMV-negative units are finally selected for IUT. If the IUT is considered an emergency, an extended matching RBC unit (if available) is selected for transfusion, regardless of its CMV status. A sample of the unit is kept, and the CMV serology will be determined with hindsight.

Since RBC units designated for IUT are leukoreduced and irradiated, the infectious potential with CMV is considered to be insignificant.

Question 11

Both strategies are applied in our institute. RBC units are routinely leukoreduced and donor's CMV antibody status is as far as possible determined before IUT transfusion, except in an emergency situation. After leukoreduction, the residual leucocyte count has to be lower than $1 \times 10e6$/unit.

Question 12

No, the sickle status of RBC units intended for IUT is not tested.

Question 13

Iso-haemagglutinin titres are not assessed for IUT transfusion since RBC units are systematically plasma reduced.

Blood product preparation

Question 14

The blood products, with all necessary analyses, are prepared by the blood supplier. However, the laboratory of the blood supplier resides within the hospital to guarantee a fast and reliable blood product supply.

Question 15

All RBC units designated for an IUT are plasma reduced and saline replaced. Since mostly 0 Rhesus negative RBC units are used, plasma removal allows eliminating residual anti-A, anti-B and anti-AB antibodies. Simultaneously, the leucocyte count is decreased, thereby reducing the risk of a transfusion-associated graft versus host disease [4] (TA-GvHD).

Question 16

The technique implicates one centrifugation with removal of the supernatant in a closed system and subsequently resuspension of the red blood cells in saline. This process involves several manual manipulation steps. After plasma reduction, RBC units have to be transfused within a delay of 24 h.

Question 17

After plasma reduction and resuspension in saline, the haematocrit value has to reside within 0·70–0·85. If the haematocrit value is lower than expected, the product is not delivered. By contrast, if the haematocrit exceeds 0·85, the physician in charge decides if the RBC unit is suitable for transfusion.

Question 18

All plasma reduced RBC units intended for IUT are irradiated and have to be transfused within 24 h. Systematic leukodepletion as well as irradiation of RBC reduces the risk of TA-GvHD, as a report indicated a TA-GvHD in a foetus receiving maternal non-leuko depleted, non-irradiated blood in 2012 [3]. The irradiator is located within the hospital in the operating area of the blood supplier.

Question 19

No other requirements have to be met for IUT.

Blood product administration

Question 20

We use the algorithm from perinatology.com (http://perinatology.com/protocols/rhc.htm).

Question 21

Yes, they are warmed up in a water bath.

Transfusion monitoring and traceability

Question 22

There have been no reports of transfusion reaction related to IUT in our institution. In 2019, one case of intrauterine foetal death occurred 6 h after the 3rd IUT for severe RhD allo-immunisation. No complications occurred during transfusion, Hb increased from 88 to 151 g/l and Ht from 27 to 46. At autopsy, a blood clot in the umbilical cord vessel was identified on the foetal side, far from the site of transfusion (at the placental side).

Question 23

Regarding the immunohaematology laboratory, a link is made between the foetal transfusion and the newborn, since every RBC unit transfused to a newborn who received a former IUT has to be irradiated until 6 month after birth.

On the clinical side, the maternal file is linked to the neonatal chart.

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Professor David Baud
Materno-fetal and Obstetrics Research Unit
Department "Femme-Mère-enfant"
University Hospital
Rue du Bugnon 21
1011 Lausanne, Switzerland
Telephone: 0041 21 314 3953
Email: David.Baud@chuv.ch

Dr. med. Giorgia Canellini
Interregional Blood Transfusion SRC
Rue du Bugnon 46
1011 Lausanne, Switzerland
Telephone: 0041 21 314 65 94
Email: Giorgia.Canellini@chuv.ch

Tobias Gleich-Nagel, PhD
Interregional Blood Transfusion SRC
Rue du Bugnon 46
1011 Lausanne, Switzerland
Telephone: 0041 79 556 52 78
Email: Tobias.Gleich@chuv.ch

Oscar Walter Torres & Patricia L. Rey

Argentina

Indication for IUT

Question 1

The IUT is only carried out as part of the treatment for haemolytic disease of the foetus and newborn (HDFN) caused by red cell alloimmunization. Sometimes as the only treatment, and also associated with high doses of intravenous immunoglobulin (400 mg/kg daily for 5 days).

Question 2

1-Anti-D (sometimes associated with anti-C or anti-E).

Question 3

We performed 7 IUT. In one patient, it was necessary to repeat a procedure 20 days after.

Blood sample testing

Question 4

Our protocol for IUT does not include taking a blood sample previous IUT. The technique performed is intraperitoneal, sometimes the liver via.

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

We always use group 0 RBC (Negative antigen for the maternal antibody).

Question 6

All the units provided are collected from voluntary blood donors.

Question 7

We only consider the maternal alloantibody at the moment to choose the blood group for IUT. We have never had a severe case of HDFN caused by anti-K1. (Among 70 000 pregnant women controlled in the last 10 years.)

Question 8

We use to provide RBC collected no more than 72 h previous to the IUT. Just once, we used a unit with 10 days of age, even so the foetal haemoglobin reached the desired value

Question 9

Although we use blood bags with mannitol solution, this additive is removed from the RBC prior to IUT.

Question 10

Yes, the CMV status is considered. We have to use blood product for preventing the blood transfusion infection.

Question 11

Our national guidelines recommend leukoreduction for IUT and exchange transfusion [5,6].

Question 12

Our current regulation does not consider necessary to investigate the sickle status, since the frequency of Sickle Cells Disease in our country is very low [6].

Question 13

We do not consider necessary to investigate iso-haemagglutinin titres. It is not done in our country.

Blood product preparation

Question 14

The RBC is prepared in our hospital, except the irradiation, which is carried out in other institution.

Question 15

No, we use RBC without any special modification.

Question 16

The red cell concentration is made by centrifugation.

Question 17

The centrifugation is carried out in order to reach a haematocrit 80–83%.

Question 18

The unit for IUT is sent to other institution for the irradiation. Doses: 25/30 Gy.

Question 19

No, there are not any.

Blood product administration

Question 20

The calculation depends on the technique used for IUT.

Intraperitoneal Technique: (Gestational Age – 20) × 10 = ml RBC required

Intravascular Technique: the ml of RBC required is calculated by:

(1) Determining the foetal and placental total blood volume by multiplying the ultrasound-estimated foetal weight (in grams).
(2) Multiplying this amount by the difference in post-transfusion (desired) and pre-transfusion Ht. and
(3) Dividing the resulting amount by the Ht. of the RBC unit [7]

Question 21

The units are warmed prior infusion only.

Transfusion monitoring and traceability

Question 22

In the last 20 years, there were no severe foetal events that forced the procedure to be suspended (dead foetuses, premature rupture of membranes).

The cases that were documented only refer to mild and brief foetal bradycardia, caused by the infusion of RBC greater than those recommended by the clinical guidelines. These events reversed in a few minutes after modifying the flow, this allowed continuing the procedure without other complications.

Question 23

All newborns with severe HDN have a programmed delivery. This means that the birth is coordinated in accordance with the Neonatology Service. Thus, during reception of the neonate, it is well known, the number of IUT received, as well as the Ht. and foetal Hb. values, weight and confirmed lung maturation.

As a rule at the Neonatal Intensive Care Unit, it must be documented the transfused volumes and the number of UTIs done, in order to know the values of the Ht. and Hb. in cord blood due to the possibility of transfusion therapy (transfusion of RBC or/and an exchange transfusion).

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Oscar Walter Torres
Transfusion Medicine Unit
Hospital Materno-Infantil Ramón Sarda
Esteban de Luca 2151
City of Buenos Aires, Argentina
Telephone: +54114308-0802
Email: owtorres@gmail.com

Patricia L. Rey
Obstetric Immunohematology Section
Hospital Materno-Infantil Ramón Sarda
Esteban de Luca 2151
City of Buenos Aires, Argentina
Telephone: +54114308-0802
Email: patricialrey@yahoo.com.ar

Carolina Bonet Bub, José Mauro Kutner & Lilian Castilho

Brazil

Indication for IUT

Question 1

In our institution, indications for IUT are red cell alloimmunization, foetal anaemia due to parvovirus, feto-maternal haemorrhage, foetal-foetal transfusion, alpha thalassaemia and foetal tumours with intrauterine bleeding [8].

Question 2

For the sporadic cases of red cell alloimmunization, we have, in our institution, the common antibodies considered to be clinically significant for IUT are anti-D, anti-c, anti-C and anti-E.

Question 3

During the year of 2018, we did not perform any case of IUT. Our annual mean of IUT is 1, in a global transfusion mean of 900/year.

Blood sample testing

Question 4

We do not perform immunohaematological tests on foetal blood samples acquired prior to an IUT but we perform ABO typing, RhD typing and Rh and K antigen phenotyping on the mother samples as part of pretransfusion testing.

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

We always provide group O RhD-negative red blood cell (RBC) units and AB plasma for IUT.

Question 6

The units transfused for IUT are allogeneic donor units, recently collected, not exceeding 5 days of collection, irradiated and inline filtered.

Question 7

Red blood cell units selected for IUT are RhD and K negative and antigen negative for any maternal antibodies to blood group antigens.

Question 8

We select RBC components recently collected for an IUT product with no more than 5 days of collection.

Question 9

Our RBC units have added SAG-Mannitol additive solution; however, for the preparation of IUT product, the additive solution is extracted.

Question 10

The CMV status of the product is not assessed and selected, once we use in line leukoreduction filters.

Question 11

We perform in line leukoreduction to prevent CMV transmission.

Question 12

The sickle status of the unit is always tested, and the unit is not selected if the test is positive [9].

Question 13

No, iso-haemagglutinin titres are not assessed for the units.

Blood product preparation

Question 14

In our institution, the blood product preparation for IUT is carried out by the blood supplier that is also a hospital transfusion laboratory.

Question 15

Red cell units have SAG-Mannitol preservative removed by centrifugation at 5526 g for 7 min at 4°C and the expected final haematocrit is up to 75%. After that, the red cells are reconstituted with AB plasma with a final

haematocrit around 55–60%, but never exceeding 75%. The final target haematocrit decision is always shared with the neonatologist. This is performed for all IUT.

Question 16

The red cell concentration method we use is manual.

Question 17

The target haematocrit of the final product is around 60%, but never exceeding 75%. The final haematocrit target decision is always shared with the neonatologist.

Question 18

Yes, the units are irradiated prior to issue and the irradiator is on site.

Question 19

No other special donor unit attributes are required for IUT.

Blood product administration

Question 20

The calculation used to determine the dose or volume required when ordering RBC for IUT depends on the gestational age of the foetus:

Foetuses with gestational age less than 24 weeks: Acute correction of foetal anaemia is associated with profound hemodynamic changes. Anaemic foetuses between 18–24 weeks have a high risk of mortality after transfusion. Thus, the post-transfusion haematocrit should not exceed 25% or the haematocrit should be increased by a maximum of four times the pre-transfusion value. A second intrauterine transfusion can be done within 48 h to bring the haematocrit to normal levels, and the next procedure should be scheduled within 7–10 days.

Foetuses with gestational age above 24 weeks: The transfusion volume depends on the initial foetal haematocrit, the size of the foetus, the haematocrit of the units to be transfused and the target (final) haematocrit. After 24 weeks, the target haematocrit is 40–50% (normal foetal haematocrit is 37 ± 4% at 17 weeks, rising to 43 ± 7% at term). We avoid transfusing with a target haematocrit >50%. The formula we use to calculate the volume to be transfused is:

$$\text{Volume to be transfused} = \frac{\text{Fetoplacental volume (ml)} \times (\text{final haematocrit} - \text{initial haematocrit})}{\text{Haematocrit of the unit to be transfused}}$$

where: Fetoplacental volume = (Foetal weight(-grams) × 0·14)

Question 21

The products are not infused at 4°C. As there is no device for heating very small volumes, we leave the blood component at room temperature for a few minutes before transfusion. The temperature does not exceed 30°C [10].

Transfusion monitoring and traceability

Question 22

No transfusion reaction in the foetus during or following IUT has ever been documented.

Question 23

If the baby is born in our institution, the IUT treatment is linked to the neonatal record after birth. As IUT cases are sporadic, it is registered manually after birth.

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Carolina Bonet Bub, MD, PhD
Hemotherapy and Cell Therapy Department,
Albert Einstein Hospital
Albert Einstein Av, 627 -3th Floor
05651-901, São Paulo, Brazil
Telephone: +551121513529

José Mauro Kutner, MD, PhD
Hemotherapy and Cell Therapy Department,
Albert Einstein Hospital
Albert Einstein Av, 627 -3th Floor
05651-901, São Paulo, Brazil
Telephone: +551121513529

Lilian Castilho, PhD
Hemotherapy and Cell Therapy Department, Albert Einstein Hospital
Albert Einstein Av, 627 -3th Floor
05651-901, São Paulo, Brazil
Telephone: +551121513529
Blood Bank, State University of Campinas
Carlos Chagas Street, 480
13083-878,São Paulo, Brazil
Telephone: +551935218705

Nabiha H. Saifee, Meghan Delaney & Theresa Nester

United States of America

Indication for IUT

Question 1

Red cell alloimmunization, foetal parvovirus B19 infection, twin/twin transfusion syndrome (TTTS), twin anaemia polycythaemia sequence (TAPS) and anaemia of unknown aetiology are indications for intrauterine transfusion at the hospitals our institution serves. Other indications for transfusion may include severe fetomaternal haemorrhage and foetal blood sampling procedure for severe foetal anaemia.

Question 2

The most common antibodies are anti-D, anti-c and anti-K, but we have also performed IUT with combination of anti-C,D,G,E and combination of anti-Fya, Jkb, and D.

Question 3

18 supernatant removed RBCs were prepared for IUT by our institution in 2018. Of these, 1 patient required 6 IUTs and 2 patients required 3 IUTs.

Blood sample testing

Question 4

Foetal blood samples are generally not obtained for testing prior to an IUT. ABO and RhD typing are performed on maternal sample. Red cell antigen phenotyping is generally performed on maternal sample only for cognate antigen for known red cell antibody. The main test performed just prior to IUT is foetal haemoglobin level so that the amount of blood product to be transfused can be determined.

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

In most cases, a supernatant removed Group O RBC is provided. At our institution, RBC units are generally not reconstituted for IUT.

Question 6

Allogeneic (donor) units are used unless mother has antibody to high frequency antigen and then autologous RBC unit may be used.

Question 7

Red blood cell units are usually only antigen negative for the maternal antibody and not antigen matched for any other red cell antigens.

Question 8

Red blood cell units selected for intrauterine transfusion are generally <7 days from collection.

Question 9

Red blood cell units in AS-3 (Nutricel®) are used at our institution.

Question 10

A CMV-negative RBC unit will be selected for intrauterine transfusion when possible.

Question 11

All RBC units are leucocyte-reduced, and some centres we serve accept leucocyte-reduction alone for prevention of CMV transmission. However, other hospitals require both anti-CMV antibody testing and leucocyte-reduction.

Question 12

Yes, all RBC units for intrauterine transfusion are tested for haemoglobin S and only selected if haemoglobin S negative.

Question 13

No, iso-haemagglutinin titres are not assessed.

Blood product preparation

Question 14

We are the blood supplier and have a centralized transfusion service that carries out blood product preparation for IUT.

Question 15

Yes, the RBC units are modified. The red cells are centrifuged, and then, supernatant is manually extracted. The units are generally not reconstituted.

(a) The RBC units are modified with supernatant removal for all intrauterine transfusions. RBCs may be washed if an autologous maternal RBC unit was collected due to the presence of antibody to high incidence red cell antigen.
(b) The RBCs are not reconstituted prior to IUT.

Question 16

A manual red cell concentration method is used.

Question 17

The HCT of the supernatant removed RBC is ~80%, and some providers may choose to add saline during IUT to reach target HCT 70%. Generally, a HCT of 70–80% is accepted for IUT.

Question 18

The supernatant removed RBC is irradiated at the blood supplier/centralized transfusion service prior to issue and sent to hospital. For the 2 main hospitals performing IUT, one transfusion service has an irradiator on site, and one does not.

Question 19

No other special attributes are required. Answers above already discussed required attributes (less than 7 days from collection, haemoglobin S negative, CMV-reduced-risk, irradiated, supernatant removed/washed).

Blood product administration

Question 20

Generally, a single RBC unit is ordered for intrauterine transfusion. The obstetrician determines the volume to be transfused. For foetuses >24 weeks gestational age, an equation from Giannina *et al.* may be used. This equation multiplies the estimated foetal weight in grams by transfusion coefficients that achieve a specific haematocrit increment assuming a donor RBC haematocrit of 75% and fetoplacental volume of 0·1 mg/g. Another equation that may be used is from Mandelbrot *et al.* based on estimated foetal weight and desired haematocrit increment and estimated donor RBC component haematocrit.

Calculation 1: For intravascular transfusion based on Giannina *et al.* [12]

$$\text{Transfusion Volume (ml)} = \text{Estimated Foetal Weight (g)} \times \text{Transfusion Coefficient}$$

Desired increment in haematocrit, %	Transfusion Coefficient
10	0·02
15	0·03
20	0·04
25	0·05
30	0·06

Calculation 1 assumes donor RBC component haematocrit of 75% and fetoplacental volume of 0·1 ml/g.

Calculation 2: For intravascular transfusion based on Mandelbrot *et al.* [13]:

$$\text{Transfusion Volume (ml)} = \frac{\text{EFW (g)} \times 0{\cdot}14\ \text{(ml/g)} \times (\text{Desired foetal HCT} - \text{Initial foetal HCT})}{\text{Donor RBC component HCT}}$$

where EFW = estimated foetal weight in grams; HCT = haematocrit.

Question 21

Blood products are aliquoted into syringes and brought to room temperature. A blood warmer is not generally used.

Question 22

No, a transfusion reaction in the foetus or following IUT has not been documented at our institution.

Question 23

No, the IUT details are not directly linked to the neonatal record after birth, but the mother's identifiers may appear as a comment in neonate's chart if any tests were performed on neonate after birth.

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Nabiha H. Saifee, MD, PhD
Seattle Children's and Bloodworks Northwest
4800 Sand Point Way NE, M/S OC.8.720
Seattle, WA, 98105 USA
Telephone: 206-987-8013
Email: NHuqSaifee@BloodworksNW.org

Meghan Delaney, DO, MPH
Children's National Hospital
111 Michigan Ave NW
Washington, DC 20010 USA
Telephone: 202-476-5124
Email: mdelaney2@childrensnational.org

Theresa Nester, MD
Bloodworks Northwest
921 Terry Avenue
Seattle, WA 98104 USA
Telephone: 206-689-6511
Email: theresan@bloodworksnw.org

Agneta Wikman & Eleonor Tiblad

Sweden

Indication for IUT

Question 1

Red cell alloimmunization
Foetal anaemia due to parvovirus
Feto-maternal haemorrhage
Foetal-Foetal transfusion
Alpha thalassaemia

We perform IUT for all kinds of severe foetal anaemia, independent of the pathogenesis. In addition to the indications above, we have performed IUT for other inherited disorders of haematopoiesis, bone marrow disorders and haemoglobinopathies.

Question 2

Anti-D, Anti-K, Anti-U, Anti-c (in that order)

Question 3

54 – IUT treatment is centralized to one national centre in Sweden, which is the Center of Fetal Medicine, Karolinska University Hospital.

Blood sample testing

Question 4

ABO typing
RhD typing

In addition to ABO and RhD typing, we perform DAT and typing of the antigens corresponding to the maternal antibody/ies on cord blood before the IUT. We perform genotyping if the results are unclear or need confirmation.

Foetal RHD genotyping in maternal plasma is done when anti-D antibodies are detected (and in all RhD-negative pregnancies). Foetal RHCE in maternal plasma is done in case of anti-c and if the father is heterozygous for the c antigen and foetal KEL in maternal plasma in case of anti-K and if the father is heterozygous for the K antigen.

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

We always use blood group O red cells suspended in saline.

Question 6

We use allogeneic units for IUT. In a few rare cases with antibodies towards public antigens (e.g. combination of anti-U + anti-D and anti-U + anti-e), we have used maternal washed red cells.

Question 7

In addition to negative for corresponding antibodies, we routinely match for maternal Rh-, K-, Duffy- and Kidd type, if possible.

Question 8

Red blood cells used for IUT are less than 5 days.

Question 9

We wash the RBCs free from SAGM solution and suspend them in saline.

Question 10

We do not test for CMV. We use lekoreduced RBCs.

Question 11

See response to question 10, we use lekoreduced RBCs.

Question 12

No not routinely, but it has been done in sickle cell patients with relatives donating matched blood.

Question 13

We do not assess ABO-titres in RBC units.

Blood product preparation

Question 14

The blood product preparation is done in the hospital transfusion laboratory, in the centre where all IUT in Sweden are done.

Question 15

All IUT units are washed and resuspended in saline
(a) All IUT units are washed and reconstituted in saline.
(b) Saline.

Question 16

Automated with Haemonetics ACP 215.

Question 17

The target haematocrit is 75–85%

Question 18

The units are irradiated immediately prior to use, in the irradiator located in the blood bank.

Question 19

No, we use fresh, antigen-matched, blood group O units.

Blood product administration

Question 20

Since the red cells for IUT usually have a haematocrit of 80% or higher, we do not use a specific calculation. We calculate the total foetal blood volume from estimated foetal weight (100 ml/kg) and aim to transfuse about 40% of estimated total foetal blood volume to achieve a post IUT foetal haematocrit of 45%.

Question 21

No, they are room temperature.

Transfusion monitoring and traceability

Question 22

No.

Question 23

Information about foetal anaemia and the need of IUT treatment is documented in the neonatal records. The foetus has a unique ID number that is linked to the personal ID number the neonatal get at delivery. The foetal ID number and the neonatal personal ID number are also linked in the blood database, with a linkage also to the maternal ID.

Agneta Wikman MD, PhD
Clinical Immunology and Transfusion Medicine
Karolinska University Hospital
141 86 Stockholm, Sweden
Telephone: +46736204601
Email: Agneta.wikman@sll.se

Eleonor Tiblad, MD PhD
Center for Fetal Medicine
Karolinska University Hospital
14186 Stockholm, Sweden,
Telephone: +46-709821752
Email: eleonor.tiblad@sll.se

Luca Pierelli, Antonella Matteocci & Maddalena Maresca

Italy

Indication for IUT

Question 1

Red cell alloimmunization
Foetal anaemia due to parvovirus
Feto-maternal haemorrhage
Foetal-Foetal transfusion
Alpha thalassaemia
All of the above are indications for the IUT; however, red cell alloimmunization is the most frequent.

Question 2

The necessity of IUT depends on the seriousness of the foetal anaemia, anyway anti-D is the most common antibody involved in serious HDFN in which IUT are indicated.

Question 3

8 IUT.

Blood sample testing

Question 4

We usually perform ABO, RhD, RhCE, Kell typing. The phenotyping of erythrocyte antigens different from those indicated above is performed only if they are involved in HDNF. We study red cell genotyping to confirm uncertain serologic result or when a specific antisera is not available (e.g. high frequency antigen).

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

Group O red cells and, if necessary, AB plasma.

Question 6

Usually allogenic (donor) units. We use unit collected from the mother only if the mother has an antibody against high frequency antigen for which is very difficult to find allogenic red cell unit provided that the mother's haemoglobin is sufficient to tolerate the phlebotomy and the foetal blood group is compatible with maternal ABO type.

Question 7

The units are routinely Group O, Kell negative and antigen matched to the mother for RhD, RhCE and, when possible, also for Duffy, Kidd and MNS antigens.

Question 8

Usually within five days from collection.

Question 9

SAG-M.

Question 10

In Italy, all allogenic red cell unit are leukoreduced.

Question 11

The CMV safe blood product status is obtain by leukoreduction, anyway we use serologic CMV-negative unit if available.

Question 12

No.

Question 13

No, because all the unit for IUT are leukoreduced, washed with saline and concentrated to obtain high Hct.

Blood product preparation

Question 14

By our hospital transfusion laboratory.

Question 15

We wash with 0·9% NaCl saline solution, and then, we concentrate the unit to obtain Hct~ 80%, except when different Hct is request from gynaecologists who carry out the IUT.
0·9% NaCl saline solution

Question 16

Manual.

Question 17

Usually Hct ~80%, except when different Hct is request from gynaecologists who carry out the IUT

Question 18

Yes, all the units for IUT are always irradiated prior to issue.

In our institution, the irradiator is in the transfusion laboratory.

Question 19

No.

Blood product administration

Question 20

$$\text{Volume IUT} = \frac{\text{Fetoplacental volume} \times (\text{Ht post} - \text{Ht pre})}{\text{Ht donor blood}}$$

Question 21

No.

Transfusion monitoring and traceability

Question 22

Yes, only one case of transient bradycardia.

Question 23

The neonatal records are linked to mother's transfusion history in which the units used for IUT are reported.

Luca Pierelli
Transfusion Medicine
San Camillo Forlanini Hospital
00152, Rome, Italy
Department of Experimental Medicine
Sapienza University
00161, Rome, Italy
Telephone: +390658703500
Email: luca.pierelli@uniroma1.it

Antonella Matteocci
Transfusion Medicine
San Camillo Forlanini Hospital
00152, Rome, Italy
Telephone: +390658703500
Email: matteocci31@gmail.com

Maddalena Maresca
Servizio di Emotrasfusione
Istituto di Ematologia-Fondazione Policlinico
Universitario
"A. Gemelli" -IRCCS
00168, Rome, Italy
Telephone: +39063051195
Email: maddalena.maresca@policlinicogemelli.it

Emeline Maisonneuve, Anne Cortey & Jean-Marie Jouannic

France

CNRHP is an acronym for National reference centre in perinatal haemobiology, dedicated in France to the management of red blood cell incompatibilities and severe jaundice. Among the dedicated missions by the ministry of health, the clinical and biological team of CNRHP are managing 300–500 follow-ups of immunized pregnancies per year for the national territory and performs 70–80 IUT per year for referred pregnancies, in the multidisciplinary perinatal diagnosis centre of Trousseau Hospital in Paris.

As shown by a recent survey, the IUT activity of CNRHP represents 40% of the whole IUT declared activity in France and the answer to this questionnaire will be the reflect of our experience [14].

Indication for IUT

Question 1

The principal aetiology of severe foetal anaemia requiring IUT was haemolytic disease of the foetus (69% of the aetiologies) with anti-RhD being the most prevalent antibody. The second aetiology was represented by parvovirus B19 infection (17% of IUTs) [14,15].

The following causes of foetal anaemia are indications for IUT in CNRHP institution:

Red cell alloimmunization, foetal anaemia due to B19 parvovirus (and cytomegalovirus), feto-maternal haemorrhage, foetal anaemia of the surviving co-twin following intrauterine death in twin monochorionic pregnancy and anaemia of unknown cause at the first act. The aetiological assessment in the absence of alloimmunization is performed prior to the transfusion and includes the diagnosis of dyserythropoiesis or other constitutional red cell disease [15].

The CNRHP performs IUT in case of spontaneous Twin anaemia polycythaemia sequence (TAPS) in twin monochorionic pregnancy, but never performs IUT in TAPS within a context of Twin-to-Twin Transfusion Syndrome, because there are two other perinatal centres in Paris dedicated for this pathology.

Question 2

The most common maternal antibodies linked with IUT in CNRHP are in order of decreased frequency: anti-RH1 (Anti-D) and anti-RH1+RH2, (Anti-D + Anti-C), anti-KEL (KEL1 (anti-K) mostly and KEL3 (anti-Kpa), anti-RH4 (anti-c), anti-Jra and anti-M.

Question 3

73 IUT were performed by the CNRHP in 2018 in 27 women, with an average of 2·7 IUT per pregnancy (minimum 1 and maximum 6).

Blood sample testing

Question 4

- Prior to the first IUT, blood is drawn from the foetus to allow the following tests:
  - point of care determination of haemoglobin (hemocue® device)
  - Kleihauer-Betke test
  - ABO and RH Kell typing, DAT, and elution
  - blood cell count (including formula and reticulocytes count) and blood smear
  - bilirubin (total and conjugated) and complete liver test and ferritin
  - sodium and potassium levels
  - G6PD, PK and electrophoresis of Hb
  - if unknown cause anaemia: ektacytometry and EMA and virology (PCR and viraemia)
  - if parental consent (agreement):karyotype

- Prior to each subsequent IUT, following blood tests are performed:
  - point of care determination of haemoglobin (hemocue® device)
  - Kleihauer-Betke test
  - DAT, and elution
  - blood cell count (including formula and reticulocytes count) and blood smear
  - bilirubin (total and conjugated) and complete liver test and ferritin
  - sodium and potassium levels
- At the end of each IUT, following blood test are performed:
  - point of care determination of haemoglobin (hemocue® device)
  - Kleihauer-Betke test
  - blood cell count
  - sodium and potassium levels

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

The requirement (respecting HAS recommendations [4]) is packed RBC of group O, Kell negative, free of iso-haemagglutinins, respecting at least maternal RH Kell phenotype and if possible extensive MNS + JK + Fy maternal phenotype (to avoid additional maternal immunization).

Question 6

The transfused blood products for IUT in our centre are exclusively packed red blood cell (RBC) leukoreduced. They are delivered by the French national blood bank (Etablissementfrançais du sang (EFS)), in accordance with the French transfusion good practises.

All delivered packed RBC are allogenic (donor) units. The only exception is the case of anti-public immunization requiring rare blood. The choice is to use frozen washed blood from the French rare blood bank via the national centre of rare blood group mainly allogenic or collected from the mother (during pregnancy or before, then frozen).

Question 7

Kell negative, free of iso-haemagglutinins, respecting at least maternal RH Kell phenotype and if possible extensive MNS + JK + Fy maternal phenotype (to avoid additional maternal immunization).

Question 8

Less than 5 days old

Question 9

Volume reduction when blood collection is done on SAG-Mannitol preservative solutions. Occasionally, RBC collection is made on CPD avoiding volume reduction but it is not often due to reduction of the lifetime of the packed RBC.

No additive solutions are used for IUT of RBC.

Question 10

The transfused blood products for IUT in our centre are exclusively packed red blood cell (RBC) leukoreduced. They are delivered by the French national blood bank (Etablissement français du sang (EFS)), in accordance with the French transfusion good practises.

The CMV status is most of the time not known and the qualifier "CMV-negative" is not a requirement because all packed RBC are leukoreduced. (HAS recommendations 4 [16]).

Question 11

The CMV status is most of the time not known and the qualifier "CMV-negative" is not a requirement because all packed RBC are leukoreduced. (HAS recommendations 4 [16]).

Question 12

Sickle cell disease is not tested on the units because in France haemoglobin level is tested in donor prior to donation. The donor needs to fulfil a haemoglobin level of 12 g/dl before collection, and in case of sickle cell disease, the Hb level is lower than this limit. This screening avoids collection of sickle disease RBC.

Question 13

Free of iso-haemagglutinins.

They are cross-matched negative with maternal plasma (of less than 72 h).

Blood product preparation

Question 14

Overview of the organization of French blood bank (EFS)

In France, all blood products are delivered by the French blood bank (named EtablissementFrançais du Sang = EFS). EFS is organized in centralized regional centres (one at least one per region and 5 for Paris region) for collection of blood products, test their eligibility, transform (irradiation, volume reduction...) that provides the different blood banks of the region; usually one

in each public hospital (that provides the private hospital nearby). In these "local" blood banks, blood is cross-matched if necessary and all the immune-haematological screening are performed for the patients (EFS laboratory of the hospital site).

In case of need of packed RBC of rare blood group, there is in France only one EFS rare blood bank, localized near Paris centralizing donors and frozen blood of rare blood group and which will do all the necessary transformation and preparation if frozen RBC units are required. The order of thawing and management of "stock" and donors of the rare blood bank is centralized by CNRGS (Centre National de Référence pour les Groupes Sanguins) working in tight coordination with the rare blood group bank.

Question 15

Haematocrit requirement of the packed red blood cells is 70–80% requiring a step of volume reduction when blood collection is done on SAG-Mannitol preservative

(a) See above.
(b) No additive solution is used for IUT of RBC.

Question 16

The volume reduction is the method of red cell concentration and is automated and done in main regional EFS centres.

Question 17

Haematocrit requirement of the packed red blood cells is 70–80% requiring a step of volume reduction when blood collection was done on SAG-Mannitol preservative solutions. Occasionally, RBC collection is made on CPD avoiding volume reduction; but it is not an often practice of EFS due to reduction of the lifetime of the packed RBC (21 days instead of 42 days). No additive solution is used for IUT of RBC.

Question 18

Units are irradiated within 24h00 prior to IUT. (HAS recommendations 3 [16]). Irradiation is done in the main regional EFS after collection and other preparation then the packed RBC is transported to the local EFS centre of the hospital where it will be used.

Question 19

They are cross-matched negative with maternal plasma (of less than 72 h).

Blood product administration

The infusion of RBC is done using a 4 four-way faucet (like in neonatal exchange transfusion) connected to an infusion fitting wire itself connected to a needle (120 mm; 20 G) by serial 2–5 ml volume infused. The packed RBC are not warmed neither prior or during the infusion, as the warming from 4°C storage temperature is happening by itself along the circuit between the packed RBC to the umbilical vein.

Prior to the beginning of blood infusion, haemoglobin level is assessed with hemocue® (extemporaneous determination) on a blood sample. This level allows us to confirm anaemia and to fix the target level, in reference to published data for each gestational age [16]. The correction should not exceed twice the initial haematocrit level.

After a series of five infusions, the Hb level is checked to adapt the volume to infuse to reach the final target level. The infusion is stopped when the hemocue® check of Hb reaches the goal.

Question 20

Our experience and review of all the IUT data of the centre done in coordination with EFS give us the subsequent volume prescription data:

- <26 weeks of gestation: 50 ml
- from 26 to 28 weeks of gestation: 80 ml
- >28 weeks of gestation: one unit packed RBC, which contains 150–180 ml with haematocrit of 70–80%

Question 21

The packed RBC are not warmed neither prior or during the infusion, as the warming from 4°C storage temperature is happening by itself along the circuit between the packed RBC to the umbilical vein.

Transfusion monitoring and traceability

Question 22

Among the last 15 years, we deplore only one transfusion reaction after or during IUT: one RBC overload in a 23 WG foetus severely anaemic after five infusions of 3 ml RBC 75% Haematocrit.

Question 23

In France, traceability of all transfusions is in charge of the prescriber of the blood products, stored in the patient file for 30 years. It is also transmitted to EFS blood bank and archived there, registered on the personal receiver computerized file.

As the foetus has no civil status, it is registered in the EFS file to be a receiver of blood product and securizes the delivery with an alias: Name: name of the mother; First name: Foetus followed by the year of the first transfusion (Foetus 2019, for example); Date of birth: 01/01/1850.

This identity is transformed, changed from the alias at birth, and the entire foetus file is transferred under the newborn identity.

Furthermore, a computerized link is created between the mother and the foetus then actualized after birth that secures the traceability.

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Emeline Maisonneuve, MD
Fetal Medicine Department
CNRHP clinical unit
Hôpital Trousseau
26 rue Arnold Netter
75012 Paris, France
Telephone: +33 1 71 73 86 52
Email: emelinem@yahoo.com

Anne Cortey, MD
CNRHP clinical unit
Hôpital Trousseau
26 rue Arnold Netter
75012 Paris, France
Telephone: 00 33 1 71 97 03 01
Email: anne.cortey@aphp.fr

Jean-arie Jouannic MD, PhD
Fetal Medicine Department
CNRHP clinical unit
Hôpital Trousseau
26 rue Arnold Netter
75012 Paris, France
Telephone: +33 1 44 73 51 13
Email: jean-marie.jouannic@aphp.fr

Jordi Fornells

Spain

Indication for IUT

Question 1

Red cell alloimmunization
Foetal anaemia due to parvovirus
Foetal cardiac surgery

Question 2

Anti-D (49%), Anti-D,C (26·5%), Anti-D,E (6·1%), Anti-D, K (2%), Anti-K (6·1%), Anti-c (4%), Anti-E (4%), Anti-M (2%)

Question 3

8.

Blood sample testing

Question 4

ABO typing
RhD typing
Direct antiglobulin test

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

Group O, Rh D and Kell negative. If antibody present in maternal plasma, then units are negative for the antigen recognized by the antibody.

We never reconstitute RBC with plasma.

Question 6

Units are allogeneic.

Question 7

Routinely, the units are Kell negatives.

Question 8

If possible less than 3 days. Always less than 5 days.

Question 9

We use RBC in SAG-Mannitol, and we remove most of it by centrifugation before the intrauterine transfusion (target haematocrit 75–85%).

Question 10

Yes, all the units are from donors CMV-negative.

Question 11

We use both strategies, CMV-negative and leukoreduction.

Question 12

The sickle status of the unit is not tested due to the low frequency of the trait in the Catalan population.

Question 13

No. Iso-haemagglutinin titres are not assessed because the RBC units are resuspended in SAG-Mannitol.

Blood product preparation

Question 14

The RBC component preparation is carried out by the blood supplier.

Question 15

The red cells are just centrifuged to remove most of the SAG-Mannitol a few hours before the intrauterine transfusion.

(a) For all IUT SAG-Mannitol is removed.
(b) No solution is added to the red cell product.

Question 16

Manual.

Question 17

75–85%.

Question 18

The red cell units are irradiated just prior to issue at the blood supplier site, about 30 min away by car from our hospital.

Question 19

No.

Blood product administration

Question 20

When ordering RBC for IUT, we order a whole unit. Obstetricians at the moment of transfusion calculate the volume to administer base on the expected volume of the foetus based on gestational age, the haematocrit of the foetus and the haematocrit of the unit.

Question 21

No, products are not actively warmed, just left a room temperature before proceeding to the IUT.

Transfusion monitoring and traceability

Question 22

No, we have never documented a transfusion reaction.

Question 23

The obstetricians tell the paediatricians, because in case of transfusion of the newborn, the products should continue to be irradiated up to 6 months after delivery.

Dr. Jordi Fornells
University Clinic Hospital
Biomedical Diagnostic Center
Sabino Arana 1
08028 Barcelona, Spain
Telephone: 34932279907
Email: fornells@clinic.cat

Arjan Albersen, Masja de Haas & Dick Oepkes

The Netherlands

Indication for IUT

Question 1

In the Netherlands, the Leiden University Medical Center, is the only institute performing IUTs. IUTs with RBCs are mainly performed for red cell alloimmunization, but also for foetal anaemia due to parvovirus infection. Indeed, fetomaternal haemorrhage and foetal-foetal transfusion can be indications for an IUT in our institute. Alpha thalassaemia is very rare in the Netherlands.

Question 2

Zwiers *et al.* recently reported on the characteristics of foetuses and pregnancies treated with intrauterine transfusions in the period from 1987 to 2017 [17]. In alloimmunized pregnancies, the most common RBC alloantibody specificity implicated as cause of foetal anaemia is anti-D (83% of cases), followed by anti-K (12%), anti-c (1%), other specificities are occasionally found and include: anti-E and anti-e, rarely anti-Fy(a), anti-Jk(a), anti-k, or a private antigen [17]. Previously, we reported on the risk of RBC alloantibodies to induce foetal anaemia for other specificities than anti-D and found a risk of 50% for anti-K [18,19].

Question 3

In 2018, we performed 60 IUTs.

Blood sample testing

Question 4

In alloimmunized women, we perform an ABO, Rh phenotype, K and Fy, Jk and Ss type. We also perform an antibody titre for any RBC alloantibody present. With a foetal blood sample, we perform an ABO, RhD and implicated antigen typing. We also perform a DAT. If possible, we check for the RBC alloantibody titre in the blood of the child.

Blood product selection (Red blood cell (RBC) concentrates):

Question 5

In all cases, for an IUT RBC product, we select RBcs with group O. Plasma is not added to the product.

Question 6

Since in almost all cases, Sanquin can deliver RBCs for IUT with the requested antigen match, an allogeneic donor unit is the first choice in the Netherlands.

Question 7

In general, RBC units are selected with group O and matched for Rh phenotype and K; if possible also for Fy^a, Fy^b, Jk^a, Jk^b, and S. Because a high number of group O, RhD-negative donors and also group O donors with R1R1 phenotype are extensively phenotyped including K, Fy, Jk and Ss antigens, it usually is possible to select units completely matching with the maternal typing for these antigens. However, in emergency situations, less compatibility needs to be accepted with the following order $Jk^a > Jk^b > Fy^a > S > Fy^b$. Schonewille *et al.* showed that in a 7-year period, ranging from 2007 to 2014, in 66% of cases (317 IUTs) extended matching is possible [20]. These authors found in three out of 69 women a RBC alloantibody after an extensively matched IUT and in eight of 73 women (11%) after an unmatched IUT [20]. To improve the availability of extended matched IUTs and to reduce donor exposure if repeated IUTs are demanded, Bontekoe and coworkers designed a procedure to prepare IUTs from 100 to 200 ml whole blood donations [21]. Since in the Netherlands in the recent years the availability of matched IUT RBC products is very high, this method has not been introduced.

Question 8

A RBC concentrate collected <72 h before is used for an IUT RBC product.

Question 9

To prepare an IUT RBC product, the SAGM is removed manually after centrifugation of a RBC concentrate (aged <72 h). SAGM is removed to prevent possible toxicity of the adenine component. NaCl (0·9%) is added to obtain a Hct of 0·80–0·85 l/l. The Hct of the product is tested. The IUT RBC product needs to be transfused within 6 hrs after processing.

Question 10 and Question 11

In the Netherlands, all RBC products are leucocyte-reduced by filtration. The donor needs to have a CMV-negative status. Therefore about four RBC products, group O and Rh phenotype and K and, if possible matched for maternal Jk, Fy and S antigens are selected and immediately tested for anti-CMV antibodies: the donor needs to be anti-CMV-negative.

The LUMC has an emergency IUT protocol in place (cases of life-threatening foetal anaemia), whereby the IUT units are ordered and issued to the foetus before CMV test results are known.

Question 12

The sickle status of a unit is not specifically tested for. In the Dutch donor population, carriers of sickle cell disease are rare.

Question 13

To prepare an IUT RBC product, the iso-haemagglutinin titres are not assessed.

Blood product preparation

Question 14

In the Netherlands, Sanquin Blood Supply is by law the national supplier of RBCs and therefore also the supplier of RBCs for IUT.

Question 15

The RBCs for IUT as provided by Sanquin are not modified or reconstituted at the Leiden University Medical Center.

Question 16

After centrifugation of the RBC concentrates, the SAGM is manually removed and NaCl (0·9%) is manually added.

Question 17

The target haematocrit of the final IUT RBC product is 80–85%.

Question 18

The RBCs for IUT are gamma irradiated with a minimum of 25 Gy at Sanquin Blood Bank and then sent to Leiden University Medical Center.

Question 19

For an IUT RBC product, next to CMV negativity, the donor needs to be "Parvo B19 tested," which implicates that anti-Parvo-B19 antibodies are tested positive in the donor history.

Blood product administration

Question 20

Sanquin Blood Bank prepares a standard RBC IUT product composed of 185 ml of RBC concentrate to which 22 ml of NaCl (0·9%) is added. In 1981, Rodeck and coworkers published a formula to calculate the volume of blood to be transfused to the foetus (Rodeck *et al*., Lancet 1981), which is used to calculate the amount of product transfused to the foetus.

Question 21

For IUT, the IUT RBC product is always warmed before and during transfusion.

Transfusion monitoring and traceability

Question 22

In 1987, we started with intrauterine transfusions and more than 750 women received one or more IUTs during pregnancy. In our long experience, we never observed a transfusion reaction in the foetus or the woman. However, RBC alloantibody production by the mother has been noted [20]. We recently reported on other type of adverse events in IUTs [22].

Question 23

The IUT blood product(s) is/are registered to the mother's record in the laboratory information system (LIS) when issued. Foetal diagnostics results (first blood drawn prior to IUT) are registered under a foetal record in the LIS whereby an "IUT object attribute" is added. Furthermore, the foetal record is electronically coupled to the record of the mother. When the foetus is born, the record is mutated for the correct neonatal registrations (name, sex, date of birth, etc.) whereby the foetal diagnostic results and object attributes remain intact.

- When blood is ordered for a neonate with an IUT history:
  - The LIS "IUT object attribute" ensures that only radiated and Parvo B19 tested units are issued.
  - The fact the foetal/neonatal record is coupled to the mothers record within the LIS ensures by rule that only units can be selected which are compatible with mother's allo-antibodies.
  - Other LIS parameters (age, sex) determine the preventive matching rules and compulsory crossmatch testing.
- The "IUT object attribute" is a permanent record, but its functionality (radiated and Parvo B19 tested units) is stopped automatically after nine months.

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Arjan Albersen
Specialist in Laboratory Medicine
(EuSpLM)
Leiden University Medical Center
Dept of Clinical Chemistry and laboratory medicine
Albinusdreef 2,
2333 ZA Leiden
Telephone: +31 71 5297473
Email: a.albersen@lumc.nl

Masja de Haas, MD PhD
Sanquin Diagnostic Services and Center for Clinical
Transfusion Research
Plesmanlaan 125
1066 CX Amsterdam
Telephone: +46-709821752
Email: m.dehaas@sanquin.nl

Dick Oepkes, MD PhD
Leiden University Medical Center
Dept of Obstetrics and Fetal Medicine
Albinusdreef 2,
2333 ZA Leiden
Telephone: +31 71 5262896
Email: d.oepkes@lumc.nl