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INTERNATIONAL FORUM

Vox Sanguinis

Transfusion of apheresis platelets and ABO groups

Several incidents of intravascular haemolysis caused by ABO antibodies have been reported after the transfusion of apheresis platelets across a minor ABO incompatibility. The relatively large volume of plasma in concentrates of apheresis platelets increases the risk of this complication. It therefore seemed of interest to acquire information on the occurrence of this complication as well as on the measures that are taken to prevent it.

To obtain this information, the following questions were sent to experts in the field. We obtained 16 contributions to this Forum:

Question 1. Have you seen cases of haemolysis after transfusion of apheresis platelets or, perhaps, after transfusion of pooled concentrates?

Question 2. Do you, in your country/centre, take measures to prevent haemolysis due to anti-A/B in platelet concentrates in recipients of apheresis platelets, e.g. in case HLA-, or HPA-matched platelets are required?

Question 3. If you take measures to prevent haemolysis in recipients due to anti-A/anti-B in platelet concentrates, which of the following have you adopted:

a) Only platelets from ABO-identical donors are transfused.

b) In case platelet concentrates are not ABO identical, do you determine the titre of IgM and IgG anti-A/B and do you exclude donors with titres above a critical level?

If you follow this policy:

- which technique(s) do you use to determine the titres;
- which titres do you consider to be critical;
- do you permanently exclude donors with titres above the critical level from the donor panel for transfusions to recipients whose red cells are incompatible with anti-A/B in the concentrate; and/or
- do you prefer donors with blood group A or B over donors with blood group O?

c) Do you resolve the problem by reducing the volume of plasma?

d) Do you replace the plasma by platelet additive solution?

e) Other measures?

Question 4. Since it has been clearly shown that anti-A/B in the recipient can considerably shorten the lifespan of incompatible platelets, do you use ABO-compatible platelets:

- for all patients;
- for selected groups, e.g. those with strong anti-A/B;
- or do you not take ABO groups into account?

In several countries/centres, haemolysis has been reported after the transfusion of apheresis platelets across a minor ABO incompatibility. It should be appreciated that such incidents have become rare because measures are now generally taken to prevent this complication (see below). To illustrate this point, in the USA prior to 1990, when platelets from ABO-mismatched donors were routinely administered, patients with a positive direct antiglobulin test on the red cells, an increased need of red cell transfusions and other evidence of haemolysis, were frequently seen. Since then, platelets from group O donors are rarely given to non-O recipients and incidents of posttransfusion haemolysis no longer occur. It is also suggested that there is insufficient awareness of this problem and that such incidents are under-reported (Kretschmer).

No incidents of intravascular haemolysis have been reported to occur after the transfusion of pooled platelet concentrates.

In all countries/centres, in principle, platelets from ABO-identical donors are used to prevent the accelerated destruction of ABO-incompatible platelets in the recipient as well as the destruction of red cells owing to the transfusion of ABO-incompatible plasma. If, because human leucocyte antigen (HLA)-, or human platelet antigen (HPA)-compatible platelets are required and ABO-identical donors are not available, the transfusion of apheresis platelets across a minor ABO incompatibility cannot be avoided, measures are taken in all countries/centres to prevent haemolysis in the recipients (see below). In such cases, the use of platelets from A donors for B recipients, and vice versa, is preferred over the use of O donors for recipients of another ABO blood group. Measures taken are as follows:

- the titre of anti-A/B in the donor is determined and only platelets from donors with low titres are used (see below);
- the amount of plasma is reduced to ≈ 90 ml;
- the plasma is replaced by platelet additive solution;
- the incompatible plasma is replaced by AB plasma; and/or
- the platelets are washed and resuspended in saline.

Techniques used for determining the titre of anti-A/B are: tube saline agglutination; tube saline agglutination followed by an indirect antiglobulin test; the micro column agglutination technique, an Olympus PK7200; and – in two centres – determining whether the alloantibodies are haemolytic *in vitro* or by actually determining the haemolysin titre.

Values considered to be critical are titres of > 1 : 64 to 1 : 100 for immunoglobulin M (IgM) and > 1 : 256 to 1 : 400 for immnoglobulin G (IgG) and of > 1 : 16 for haemolysins or just when haemolysis occurs *in vitro*. Evidence that the titre of the alloantibodies in the donor is indeed critical with regard to the occurrence of haemolysis in the recipient, is presented by Reinhardt: no haemolysis was found to occur with concentrates from donors with a titre of ≤ 1 : 64, whereas severe haemolysis occurred in a group A patient transfused with an apheresis concentrate from a group O donor with an anti-A titre of > 1 : 512.

Donors with high titres of anti-A/B are not excluded from the donor panel, but their platelets are not used across a minor ABO incompatibility. Heal and Blumberg draw attention to the fact that, in addition to accelerated red cell destruction, there are other disadvantages of transfusing ABO-incompatible plasma, such as the formation of immune complexes which bind and activate complement and which then bind to platelets, leading to phagocytosis by monocytes/macrophages and carrying unknown potential for morbidity e.g. proinflammatory predisposition for multi-organ failure and death in cardiac surgery. A similar remark is made by Kretschmer.

In all countries/centres, if HLA- or HPA-compatible platelets are required and no ABO-identical donors are available, ABO incompatibility is preferred over HLA or HPA incompatibility, one of the above measures being taken to prevent the problems attached to the transfusion of ABO-incompatible plasma in the platelet concentrate. However, in one centre (Novotny & Brand), when the post-transfusion platelet increment is insufficient, the titre of anti-A/B in the recipient is determined, and if found to be 1 : 128 to 1 : 256, only ABO-compatible platelets are used.

In conclusion, there is general awareness of the danger of haemolysis (and other problems) after the transfusion of apheresis platelets containing ABO-incompatible plasma. Measures to prevent this problem are taken universally, which explains why this complication now rarely occurs.

It goes without saying that the reader is advised to read the individual answers, which contain much further interesting information.

R. N. I. Pietersz
Sanquin Blood Bank North-West Region
PO Box 9137
NL-1006 AC Amsterdam
the Netherlands
E-mail: R.Pietersz@Sanquin.nl

C. P. Engelfriet
Sanquin Diagnostic Services and Sanquin Research
PO Box 9190
NL-1006 AD Amsterdam
the Netherlands
E-mail: P.Engelfriet@Sanquin.nl

H. W. Reesink
Sanquin Blood Bank North-West Region and Sanquin Diagnostic Services
PO Box 9137
NL-1006 AC Amsterdam
the Netherlands
E-mail: H.Reesink@Sanquin.nl

K. G. Davis, J. Lown & A. Thomson

Question 1

We know of at least two documented incidents of intravascular haemolysis (one involving an infant and the other an adult) after transfusion of an apheresis product. We have heard of other anecdotal cases, but they are uncommon. Most concern comes during pediatric use when cross-grouping is necessary.

Question 2

At present there is varying practice in Australia with respect to the measures undertaken to reduce the possibility of haemolysis. In some jurisdictions, buffy coat-pooled platelets are plasma reduced and resuspended in 'T-Sol'. In another jurisdiction, 100% of platelets are obtained from apheresis and are screened for 'high-titre' donor antibodies.

Question 3

a) See the response to question 4.

b) Yes in some jurisdictions. The following is an example of a method being used – sal RT progressing to the indirect antiglobulin test (IAT) for all apheresis units; a one-off dilution of 1 : 200 used, if negative = low titre; high-titre donors are not permanently excluded. Group A donors have been used instead of O for group B patients.

c) As stated above in the response to question 2, some jurisdictions produce plasma-reduced buffy coat platelet pools to avoid the haemolysis issue.

d) Yes, T-Sol is used as a plasma replacement in buffy coat pools.

e) Currently a process is underway to validate T-Sol-suspended apheresis platelets. The long-term desire is to obtain 100% plasma-depleted apheresis platelets in additive solution.

Question 4

Consideration is given to ABO (and in some instances RhD) groups. The following is an extract from national guidelines [1]:

Platelet concentrates, in order of preference, should be:

(i) Patient's own ABO, Rh(D) group.

If this is not possible, a decision on whether to give antigen or plasma-incompatible platelets may be of importance, depending on the patient diagnosis/therapy:

(ii) ABO, Rh(D) antigen compatible (but plasma incompatible), or

(iii) ABO, Rh(D) antigen incompatible.

Requirements for HLA compatibility may take precedence over ABO typing.

Individual units of different ABO blood groups shall not be pooled. Matching for Rh(D) type is desirable (as platelet products may contain small or minimal numbers of red cells), but may be less important than ABO matching. Platelets do not carry Rh antigens.

The administration of Rh(D) immunoglobulin should be considered for Rh(D)-negative patients, especially premenopausal females, when platelet concentrates from Rh(D)-positive donors are transfused.

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K. G. Davis
Chief Medical Scientist
Transfusion Medicine Unit
Institute of Medical & Veterinary Science
Royal Adelaide Hospital
Adelaide
South Australia
E-mail: ken.davis@imvs.sa.gov.au

J. Lown
Principal Scientist
Transfusion Medicine Unit
Royal Perth Hospital
Perth
Western Australia
E-mail: john.lown@health.wa.gov.au

A Thomson
Consultant Hematologist
Royal North Shore Hospital
Sydney
NSW
Australia
E-mail: Athomson@doh.health.nsw.gov.au

P. Turek

Question 1

No severe haemolysis caused by ABO incompatibility after administration of platelet concentrate has been observed during (at least) the last 10 years in our center, but a risk of haemolysis is well known from the literature (1,2,3,4).

Question 2

To prevent haemolysis we prefer to use ABO-identical or at least ABO plasma-compatible apheresis platelets in our centre (a similar policy is adhered to throughout the country). If these are not available, we take measures to reduce exposure to incompatible plasma, especially in children.

Question 3

a) The majority (≈ 85 %), but not all, patients are transfused with ABO-identical platelets, especially when apheresis platelets are used. In a group of bone marrow transplant patients with graft/recipient ABO mismatch, we respect the ABO group of the donor/graft.

b) We test all (A, B and O) apheresis donors for anti-A/B by using the agglutination test in saline (e.g. for immunoglobulin M); titres are written on the label of the product. Platelets from donors with a titre of > 1 : 64 are used exclusively for ABO-identical recipients.

In theory, when the donor's anti-A/B titre is not known, we prefer to use donors with blood group A or B rather than donors with blood group O. In practice we do not usually have to make this choice owing to the above-mentioned procedures.

About 25% of apheresis platelet concentrates in our centre are produced/delivered as 'platelets in additive solution'. We reduce plasma volume only in special situations (for small babies, etc.).

Question 4

We prefer ABO-identical platelets, except when required for refractory or immunized patients where human leucocyte antigen (HLA) or human platelet antigen (HPA) platelets are required (5). If this is not possible, we respect 'plasma compatibility', especially in children, or we reduce the plasma content, replacing plasma by additive solution. The anti-A/B titre in the recipient is taken into account only in patients after mismatch bone marrow transplantation.

In the worst-case scenario (vital indications) we use buffy coat-derived platelets of different blood groups (e.g. a set of individual bags of different ABO groups, some of which could be ABO incompatible).

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Petr Turek
Institute of Haematology and Blood Transfusion
U nemocnice 1
128 20 Prague
Czech Republic
E-mail: turek.petr@centrum.cz

E. Dickmeiss

Question 1
Minor ABO-incompatible apheresis platelet transfusions are avoided, and we have not seen haemolysis after transfusion with minor incompatible buffy coat-derived platelets pooled with additive solution.

Question 2
Yes. In recipients of apheresis platelets, we take measures to prevent haemolysis caused by anti-A/B in platelet concentrates.

Question 3
We replace the plasma with AB plasma if minor ABO incompatibility is unavoidable in human leucocyte antigen (HLA)- or human platelet antigen (HPA)-matched transfusions.

Question 4
Major ABO-incompatible platelet transfusions are avoided for all patients. However, if the only available HLA-matched platelets to a given HLA-ABC immunized patient are major ABO incompatible, we prefer to use these in lieu of ABO-compatible, but HLA-mismatched, platelets.

Ebbe Dickmeiss
Copenhagen City Blood Transfusion Service
Section 2034, Rigshospitalet
Blegdamsvej 9
DK-2100 Copenhagen
Denmark
E-mail: ebbe.dickmeiss@rh.dk

T. Krusius & J. Matilainen

The Finnish Red Cross Blood Service is an economically and operatively independent section of the Finnish Red Cross. It is responsible for the national blood programme in Finland. It collects blood from voluntary donors, manufactures blood components and plasma products, and offers laboratory services and expert consultations on transfusion medicine and organ and stem cell transplantation to hospitals. Its areas of expertise include blood group serology, platelet serology, haemostasis and tissue typing.

All platelet products that are transfused in Finland are manufactured and supplied to the hospitals by The Finnish Red Cross Blood Service. Ninety eight per cent of platelet components distributed to hospitals are pooled products, which are prepared by the buffy coat method from four whole-blood units and suspended in platelet additive solution. Plasma accounts for less than 20% of the volume of the pooled platelet products, which means that ≈ 50 ml of plasma is present in a four-donor platelet component.

Two per cent of platelet components are single-donor products, which are prepared by apheresis and suspended in donor plasma. Plasma accounts for most of the volume of apheresis platelet products, which means that ≈ 190 ml of plasma is present in an apheresis platelet component corresponding to four platelet units. Apheresis platelets are transfused almost exclusively to human leucocyte antigen (HLA)- and/or human platelet antigen (HPA)-alloimmunized patients.

Question 1
The Finnish Red Cross Blood Service collects data on the adverse effects of the transfusion of blood components in Finland. The collection system is based on voluntary reporting from hospitals and there have been no reports of haemolytic reactions caused by the transfusion of pooled or single-donor apheresis platelet products.

Question 2
We are aware of the possibility of haemolysis caused by donor anti-A/B, especially in recipients of apheresis platelets. At present we try to prevent haemolysis caused by anti-A/B in platelet components primarily by supplying ABO-identical apheresis platelet products to hospitals.

We have a donor registry of 10 100 active HLA-typed platelet donors, and for most HLA-immunized patients it is possible to find 3/4 or 4/4 HLA AB-matched platelets, which are either ABO identical or ABO compatible. Transfusion of ABO-compatible apheresis platelets is considered relatively safe because it seems that the Finnish donor population has quite low titres of anti-A and anti-B. For example, we recently determined anti-A and anti-B titres from 139 blood group O platelet apheresis donors, in tubes, by using the direct agglutination method. The median anti-A or anti-B titre ranged from 1 : 8 to 1 : 16. Only 5·7% of the donors had a titre of > 1 : 32, and none had a titre of > 1 : 128. In general, the titres were clearly lower than seen in haemolytic reactions, owing to the presence of anti-A/B in platelet concentrates published in the literature.

HPA-typed platelets are mainly transfused to neonatal alloimmune thrombocytopenia (NAIT) patients. HPA-typed platelet products are washed with AB RhD-negative plasma to prevent haemolysis caused by anti-A/B if the donor plasma is not compatible with the ABO antigens of the NAIT patient.

Question 3

The Finnish Red Cross Blood Service favours the production of group O and group A pooled platelets, and patients are almost always transfused either with ABO RhD-identical platelets or with ABO RhD-compatible platelets.Transfusions of pooled platelet components against the donor anti-A/B are also considered to be safe owing to the small amount of plasma in pooled products and also owing to the low titre of anti-A/B in the Finnish donor population.

Presently we are discussing how to reduce the potential risk of haemolysis in non-ABO identical apheresis platelet transfusions. The alternatives are to replace plasma by platelet additive solution or to screen donors for anti-A/B. So far no decision has been made regarding which alternative will be implemented.

Question 4

In Finland, all patients are transfused with ABO RhD-identical platelets whenever possible. ABO-compatible platelets are used if identical platelets are not available, and only under exceptional circumstances are ABO-incompatible platelets transfused. The anti-A/B status of the patient is not usually determined prior to platelet transfusions. Patients undergoing allogeneic stem cell transplantation are transfused only with ABO RhD-identical platelets. Exceptionally, ABO-incompatible platelets are transfused to alloimmunized patients, for example owing to a lack of ABO-compatible 3/4 or 4/4 HLA AB-matched platelets.

Tom Krusius
Medical Director
E-mail: tom.krusius@bts.redcross.fi

Jaakko Matilainen
Medical Officer
Finnish Red Cross Blood Service
Kivihaantie 7
00310 Helsinki
Finland
E-mail: jaakko.matilainen@bts.redcross.fi

V. Kretschmer & R. Karger

Question 1

The current German regulations, as a rule, require ABO-compatible platelet transfusions to be performed. The passive transmission of alloantibodies with the plasma has to be considered only in special cases. Thus, the transfusion of ABO non-identical platelets is permitted and, hence, the transfusion of ABO-incompatible platelet concentrates, especially of pooled units, is not unusual in Germany.

Many years ago, mild haemolysis occurred in a patient transfused with ≈ 300 ml of minor-incompatible apheresis platelets (donor blood group O, recipient A). In addition, several transfusion reactions without recognizable haemolysis have been reported, especially in children, which could only be explained by ABO-minor incompatibility. Following these experiences, we always administer ABO-identical or only major-incompatible apheresis platelets. Minor-incompatible platelets are only used in the event that antibodies against human leucocyte antigens (HLA) have to be taken into account if the anti-AB titres of the donor are low (see below).

Pooled platelet concentrates (from four donors) are more liberally chosen by us with regard to ABO-compatibility, as the plasma volume of every one donor is only ≈ 50 ml and the risk of including donors with high haemolysin levels is only ≈ 10%. However, we normally restrict the number of incompatible platelets to one ABO-minor incompatible pooled platelet concentrate, except in massive transfusion. Recently, a group A patient developed positive cross-matches with group A red cells and a positive direct antiglobulin text (DAT) after receiving two pooled group O platelet concentrates on one day. No haemolysis was reported to our laboratory, probably because massive transfusion followed owing to an emergency revision after surgery to replace a heart valve.

Question 2

At our institution, a clear regimen is followed in order to prevent haemolysis caused by minor-incompatible platelet transfusion, which is explained below (cf. our answer to Question 3). In addition, when transfusion reactions in patients transfused with ABO-minor incompatible platelet concentrates are reported to our laboratory, we always ask the clinicians to determine haemolysis parameters. We believe that many clinical colleagues in Germany, and possibly also in other countries, are unfortunately insufficiently aware of this problem, a matter which could explain the few reports on haemolysis caused by the transfusion of ABO-minor incompatible platelet concentrates.

Question 3

In most instances, we transfuse apheresis platelets from ABO-identical donors. To determine whether platelet apheresis concentrates are minor-incompatible, we determine the titre of immunoglobulin M (IgM) anti-A/B by using a simple agglutination tube test. Previously, we have already excluded units for minor-incompatible transfusion if titres were determined to be > 1 : 32. As no transfusion reactions have been reported for several years, we accept titres of < 1 : 100 as a critical threshold without obtaining any negative feedback. We do not believe that anti-A/B immunoglobulin G (IgG) plays a significant role in minor ABO-incompatible platelet transfusion.

We do not determine the anti-A/B titres in pooled platelets, but do restrict the number of units (see the response to Question 1). We do not exclude donors with high titres of anti-A/

B from donation either for pooled platelet concentrates or for apheresis platelets.

It is certainly preferable to use donors with blood group A or B instead of O in ABO-minor incompatible platelet transfusion. The problem of ABO-minor incompatibility has only very rarely been solved by reducing the volume of plasma. Under such circumstances we usually exchange the donor plasma for group AB plasma.

Question 4

Our transfusion regimen is designed to take fresh apheresis platelet concentrates for haematological/oncological patients with bone marrow hypoplasia. Therefore, these patients mainly receive ABO-identical concentrates. Only if HLA has to be taken into account are ABO-major- or ABO-minor incompatible apheresis concentrates used. In ABO-minor incompatibility, the critical anti-A or anti-B titre is taken into account, as described above. If the platelet increment after ABO-major incompatible platelets shows no efficacy, we search for another donor.

We administer pooled platelet concentrates in acute bleeding complications and in peri-operative and/or post-traumatic situations. Here, the choice of ABO-compatible or ABO-incompatible platelets is often driven by logistic considerations, i.e. by our aim to ensure supply.

Nevertheless, we would like to remind of reports of increased morbidity and mortality during induction therapy for acute leukaemia and allogeneic progenitor cell transplantation when ABO-mismatched platelet transfusion was performed [1–3], which could not be explained only by haemolysis. Also, in this respect ABO non-identical platelet concentrates should be used for long-term platelet therapy only when supply cannot otherwise be ensured, but not in order to use up concentrates shortly before they become out of date. An alternative is to use minor-incompatible concentrates with low or reduced anti-A/B levels. However, outcome data are still controversial in patients not requiring long-term platelet therapy [4,5].

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V. Kretschmer
R. Karger
Institute for Transfusion Medicine and Haemostaseology
University Hospital
Conradistrasse
Marburg
D-35033
Germany
E-mail: kretschv@mailer.uni-marburg.de

P. Reinhardt, M. Wiesneth, H. Schrezenmeier & E. Seifried

Question 1

In our institution, only patients with anti-human leucocyte antigen (HLA) and/or human platelet antigen (HPA) antibodies, and who are refractory to pooled random donor platelet concentrates, receive HLA/HPA-matched platelet concentrates collected by apheresis. Therefore, platelet apheresis products are prepared on individual demand only and not pre-emptively.

Between January 2004 and October 2004, overall 640 apheresis concentrates (mean plasma volume 279 ±12 ml) and more than 12 000 pooled platelet concentrates (mean volume 282 ± 25 ml containing additive solution and less than 40% residual donor plasma) were generated and distributed.

Less than 1% of the pooled platelet concentrates were given across an ABO-minor incompatibility, all others were ABO identical. Of the 640 HLA-matched apheresis concentrates, 33% were ABO-minor incompatible, 17% were ABO-major incompatible, and 50% were ABO identical.

Not a single incident of haemolysis was reported for any of the pooled or apheresis platelet products distributed. All blood products were leucocyte depleted and all apheresis donors were screened for allohaemagglutinins/haemolysins.

Question 2

For the selection of HLA/HPA-matched platelet concentrates, ABO-identical donors are favoured; however, an HLA/HPA-match is given preference. To prevent haemolysis, allohaemagglutinins/haemolysins are currently determined in the serum of all apheresis donors whose products are ABO-incompatible with the intended recipient [1,2]. The presence of haemolysins or anti-A/B titres of 1 : 128 determines that the platelet concentrate is to be used only for ABO-identical transfusion or the volume of the plasma has to be reduced and replaced by additive solution.

ABO-identical platelet concentrates are used whenever possible and are a must for the substitution of neonates and infants with a body weight of < 25 kg.

Question 3

More than 95% of our donors show allohaemagglutinin titres of < 1 : 128. We are not aware of complications associated with titres of < 1 : 128, justifying our cut-off level of > 1 : 64

for adults [2]. Titres of > 1 : 64, or positive haemolysins in the apheresis products, prompt the removal of donor plasma from the product and substitution with an additive solution, i.e. T-Sol [3]. However, there are no studies that clearly define a critical isohaemagglutinin titre [4].

The technique used to determine the anti-ABO titre is as follows. Undiluted donor serum and serial twofold dilutions in 0·9% NaCl are incubated for 5 min with test erythrocytes of blood groups O, A1, A2 and B, at +20 °C. Erythrocyte agglutination (allohaemagglutinin) is evaluated and documented after a brief centrifugation. The tubes are then incubated at +37 °C for 30 min, without a spin, and the supernatant is tested for haemolysis (isohaemolysin) [2].

In 2004, six out of 640 platelet apheresis concentrates had allohaemagglutinin titres of > 1 : 64 and the plasma of these products was reduced before transfusion, as described above. No haemolysis was reported to our institute after transfusion of platelet apheresis products during a time-period spanning the last 10 years. However, prior to routine allohaemagglutinin screening, a patient with blood group A had received a platelet apheresis concentrate of group O, resulting in severe haemolysis. Retrospective testing revealed an anti-A titre of 512 in the platelet product.

In terms of overall apheresis platelet production, there is no preference of blood group A over O because the HLA-match is given preference. Donors with high anti-A/B titres were not permanently excluded from platelet apheresis, but were tested again.

Question 4

All platelet substitutions (both pooled and apheresis concentrates) are intended to be ABO-identical. Allohaemagglutinin titres of the recipients are not determined.

If ABO-identical donors are not available, i.e. owing to high demand and/or the presence of rare blood group or multiple anti-HLA antibodies, determination of allohaemagglutinins/haemolysins in platelet apheresis products is performed to prevent haemolysis; ABO-minor incompatibility is preferred over ABO-major incompatibility [1,5].

The strategy described is successfully used also in our institutes Baden-Baden, Frankfurt, Mannheim and Kassel, which produce more than 3500 apheresis platelet and more than 55 000 pooled random donor platelet concentrates per year without reports of haemolytic transfusion reactions.

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P. Reinhardt
M. Wiesneth
H. Schrezenmeier
E. Seifried
Red Cross Blood Services Baden-Württemberg – Hessen
Institute Ulm
Helmholtzstrasse 10
D-89081 Ulm
Germany
E-mail: p.reinhardt@blutspende.de

P. Rebulla, N. Greppi, D. Riccardi & F. Morelati

Question 1

The occurrence of haemolysis after transfusion of apheresis platelets or pooled concentrates has not been reported to our blood transfusion service, from the 44 clinical wards using our platelet products, during the time-period January 2000 to November 2004, as determined by the review of 232 reports of transfusion-untoward effects to platelet products received during the same time-period. Our local lack of evidence of haemolysis, despite its intrinsic positive meaning, must be considered together with additional information on our platelet support policies, which are summarized below.

Our standard platelet product is obtained by soft centrifugation of a pool of five buffy coats diluted in 300 ml of a commercial crystalloid platelet additive solution (T-Sol; Baxter, Maurepas, France). Owing to the availability of pooled concentrates prepared from buffy-coats, we use a very limited number of apheresis platelets, which are required only during occasional shortages. In 2003 we delivered a total of 4146 platelet products, comprising 4036 (97·3%) platelet pools and 110 (2·7%) apheresis platelets. Similarly to the buffy-coat pools, our apheresis platelets are suspended in a medium consisting, on average, of 200 ml of plasma and 300 ml of T-Sol. Approximately 60% of our platelets have been white cell-reduced at the time of production by filtration and are used for selected indications including: immunodepressed patients undergoing haemopoietic stem cell transplantation; patients with non-haemolytic febrile transfusion reactions; prevention of cytomegalovirus (CMV) transmission or reactivation; and administration of human leucocyte antigen (HLA)-compatible platelets.

The main features of our platelet support policy, which are relevant to the discussion on the occurrence of haemolysis, are as follows:

(1) The prevalent use of pooled concentrates as compared to single-donor apheresis products reduces the risk that a recipient is transfused with a high ABO agglutinin-titre, single-donor product.

(2) The standard use of T-Sol reduces the absolute amount of ABO agglutinins in the platelet products.

Based on the characteristics of our platelet products, although we aim to use ABO-identical platelet transfusions whenever possible, this is not an absolute requirement. Of the 4146 products delivered in 2003, 425 pools were issued for inventory replacement to other institutions and 934 were prepared with buffy coats of different ABO/Rh groups. Of the remaining 2787, in which all buffy coats were of the same ABO/Rh group and the recipient ABO group was registered in our data management system, 237 (8·5%) were pools of group O given to A, B or AB recipients.

Question 2

We do not routinely take measures to prevent haemolysis, as outlined in answer 1. Nonetheless, we specifically ensure that an apheresis platelet product used for a neonate or for intrauterine transfusion is ABO identical. When this is not possible and the platelet product shows plasma incompatibility with the recipient, we concentrate the platelets by centrifugation and replace the plasma with T-Sol immediately before infusion.

Question 3

a) See above.

b) Whenever we believe that the titre may be important (i.e. very infrequently), it is determined by using 10 μl of 3% red blood cell (RBC) suspension and 40 μl of plasma or serum in the microcolumn agglutination technology (BioVue; Ortho Diagnostic Systems, Raritan, NJ). We define critical a titre in excess of 1 : 64 for immunoglobulin M (IgM) and in excess of 1 : 256 for immunoglobulin G (IgG), respectively [1]. We do not have a standard policy of permanent exclusion of donors from the donor panel for transfusions to recipients whose red cells are incompatible with anti-A/B in the platelet concentrate. We do not prefer donors with blood group A or B over donors with blood group O.

c) See the answers to questions 1 and 2.

d) See the answers questions 1 and 2.

Question 4

We aim to use ABO-compatible platelets for all recipients. In 2003, ABO major compatibility was achieved in 95·5% of platelet transfusions. We do not routinely determine anti-A/B titres in the recipients.

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Paolo Rebulla
Noemi Greppi
Donatella Riccardi
Fernanda Morelati
Centro Trasfusionale e di Immunologia dei Trapianti
IRCCS Ospedale Maggiore
Via Francesco Sforza 35
20122 Milano
Italy
E-mail: prebulla@policlinico.mi.it

M. Uchikawa, N. H. Tsuno, K. Takahashi & K. Tadokoro

Question 1

We have no experience regarding haemolysis after transfusion of apheresis platelets or after transfusion of pooled concentrates.

Question 2

We make it a rule to transfuse ABO-compatible apheresis platelet concentrates. However, in the case of human leucocyte antigen (HLA)- or human platelet antigen (HPA)-matched platelets, if platelet concentrates of an appropriate ABO type are not available, we perform anti-A and/or anti-B titration of donor plasma.

Question 3

In our Blood Center, we determine the anti-A or anti-B titre by using the indirect antiglobulin test after incubation at 37 °C. Using this method, a titre of ≥ 1 : 512 is suggestive of a critical titre for anti-A or anti-B. If the anti-A or anti-B in apheresis platelets exceeds the critical titre level, this is communicated to the clinicians. In this setting, some clinicians transfuse the platelet concentrate with a reduced volume of plasma, whereas others prefer not to transfuse platelet concentrates with titres above the critical level.

We try to administer platelet concentrates from group O to recipients of other ABO groups as rarely as possible. In the past year, we supplied 2362 HLA-matched apheresis platelet concentrates, 567 of which were ABO-minor incompatible. Only 4·9% (28/567) were supplied as group O to other ABO groups.

Question 4

As it has been clearly shown that anti-A or anti-B in the recipient can considerably shorten the life span of incompatible platelets, we use ABO-compatible platelets on a routine basis for all patients. However, when HLA- or HPA-matched platelets are needed, the titres of anti-A or anti-B only in the donor plasma is measured. Moreover, in emergency situations,

in which ABO-incompatible platelets are transfused, the titres of anti-A or anti-B are measured only in the donor plasma.

Makoto Uchikawa
Tokyo Blood Center Japanese Red Cross

Nelson H. Tsuno
Koki Takahashi
Department of Transfusion Medicine and Immunohematology
University of Tokyo
7-3-1 Hongo
Bunkyo-ku
Tokyo 113-8655
Japan
E-mail: tsuno-tky@umin.ac.jp

Kenji Tadokoro
National Headquarters Japanese Red Cross

V. M. J. Novotny & A. Brand

Question 1

In order to respond to the topic of ABO-incompatibility of platelet transfusions on a national level, we questioned the four Dutch blood bank divisions and the eight Dutch university hospitals for their policy and experience.

As shown in Table 1, in 2003 the blood banks delivered 31 589 platelet concentrates (PCs) to the hospitals. The majority of these PCs were prepared from a pool of five random unit buffy coats and a minority [mainly for neonates and human leucocyte antigen (HLA)-matched PCs] were prepared as single-donor apheresis platelets. Of the eight university hospitals, six responded and five provided the total number of PCs transfused. In these five hospitals, 17 621 PCs had been transfused, representing 56% of all PCs prepared by the blood banks. None of the interviewed hospitals reported haemolysis after platelet transfusion in 2003, although one hospital remarked that in 2004 a severe haemolytic transfusion reaction was observed in a child of blood group AB after transfusion of an apheresis PC of blood group O.

In 2003 the national haemovigilance foundation (TRIP) reported 186 reactions towards platelet transfusions and 697 reactions to red cell transfusions. They calculated a risk three times higher for transfusion reactions after platelet transfusion than after red cell transfusions, but none was associated with haemolysis.

Question 2 and 3

The blood bank and hospitals both aimed to circumvent (as much as possible) ABO-incompatible plasma with the PCs, but the demand could not always be met, because mainly blood group O and A PCs are prepared. There is still no national policy to determine the anti-A and/or anti-B titres in donors who contribute to buffy coat-derived or apheresis PCs. Two blood banks, providing PCs for four university hospitals, prepare PC in additive solution.

One hospital mentioned that in all PCs, incompatible plasma was removed prior to transfusion by volume reduction (to ≈ 20 ml for adults and < 10 ml for neonates). The blood bank prepared these concentrates on request. HLA/human platelet antigen (HPA)-matched platelet transfusions are more often ABO-mismatched for minor as well as for major ABO differences.

As contradicting data exists in the literature regarding platelet loss during centrifugation to remove plasma, we asked the aforementioned hospitals for clinical experience with volume-reduced PCs. They reported results on 533 matched PCs administered to 53 HLA (HPA) alloimmunized patients. In 69% (n = 368) of the transfusions, a minor ABO-incompatibility existed between the HLA-matched platelet donor and the patient. All of these incompatible transfusions were volume-reduced; the 1-h post-transfusion corrected count increment (CCI) was similar to the increment of ABO-minor compatible PCs in plasma, which were not volume-reduced. The 24-h recovery tended to be slightly lower, a decrease that was neither significant nor clinically relevant (Table 2).

Table 1 Results of the questionnaire of the Dutch blood banks and hospitals

Blood banks	***n* = 4**
PC distributed (*n*)	31 589
Preventive measures	
Use of plasma-compatible PCs	If possible
Exclude donors with high anti-A and/or B titres	No
Use of platelet additive solution	50%[a]
Reduction of the plasma volume by concentration	15%[b]
ABO antigen incompatibility measures	
ABO antigen-compatible PCs	If possible
Only when increased anti-A and/or B titres patient	No

[a]Two of the four blood banks provided platelets in additive solutions (PAS II).
[b]One blood bank, at the request of the regional university hospital.
PC, platelet concentrate.

Table 2 Results from 53 alloimmunized patients: corrected count increments (CCIs) of human leucocyte antigen/human platelet antigen (HLA/HPA)-matched platelet transfusions, either in plasma (minor ABO compatible) or volume-reduced to 20 ml prior to transfusion (minor ABO-incompatible)[a]

	PC in plasma	**PC volume-reduced**	***P*-value**
No. of transfusions	165	368	
CCI at 1 hr ± SD	13·4 ± 8·4	14·3 ± 9·3	0·31
No. of transfusions	102	184	
CCI at 24 hrs ± SD	6·9 ± 6·8	5·4 ± 6·7	0·06

[a]Personal communication, B. A. S. Tomson (Sanquin division Southwest).
SD, standard deviation.

Table 3 ABO antigen compatible vs. incompatible platelet transfusions[a]

	ABO identical and minor incompatible *n* = 79	Major incompatible *n* = 14	*P*-value
1 h CCI	12·9 (± 6·7)	8·9 (± 4·9)	0·051
24 h CCI	8·1 (± 6·7)	5·3 (± 4·7)	0·138

CCI, corrected count increment.
[a]Personal communication, J. L. Kerkhoffs (Sanquin Southwest).

Question 4

If possible, PCs are ABO-antigen matched, but in ≈ 10–20%, the transfusion is ABO-antigen incompatible.

Although PCs are ABO antigen matched as much as possible, in particular for HLA/HPA-alloimmunized patients, preemptive ABO-antigen matching further impairs the number of available matched donors. Neither for random PC nor for HLA-matched PC are the anti-A and/or B titres of the recipient routinely determined, but form part of a decision tree in the event of failure to reach a sufficient post-transfusion increment; under these cicumstances, the titre of anti-A and/or B is taken into account and if > 1 : 128 to 1 : 250, only ABO-antigen matched PCs are further administered.

In a non-selected group of patients with AML and an unknown anti-A/B titre, who participate in a randomized, controlled study comparing PAS vs. plasma-stored PCs, a lower CCI was observed, in particular 1 h after transfusion. In this study, 411 PCs were transfused, of which 79 were ABO-minor incompatible and only 14 were major incompatible. Even with these small numbers the difference was significant (Table 3).

In conclusion, overt haemolytic transfusion reactions upon ABO-minor incompatible platelet transfusions are rare. It should be noted that serological effects, e.g. development of a positive direct antiglobulin test (DAT), was not recorded and subclinical haemolysis is thus not excluded. Removal of incompatible plasma can be safely carried out without obvious impairment of platelet recovery. A policy to withhold ABO-antigen incompatible PCs should be maintained as ABO-antigen incompatiblity impairs post-transfusion increments.

V. M. J. Novotny
Department of Blood Transfusion and Transplantation Immunology
Radboud University Medical Centre
PO Box 9101
6500 HB Nijmegen
the Netherlands
E-mail: v.novotny@hemat.umcn.nl

A. Brand
Sanquin Blood Bank South West
PO Box 2184
2301 CD Leiden
the Netherlands
E-mail: anneke.brand@bloodtrd.nl

B. G. Solheim

Question 1

Haemolysis has been observed after the transfusion of apheresis platelets, but not after the transfusion of pooled buffy coat platelets (which are resuspended in platelet additive solution and ≈ 25% plasma).

Question 2

In Norway we take measures to prevent haemolysis, caused by anti-A/B in platelet concentrates, in the recipients of apheresis platelets.

Question 3

a) If available.

b) Saline agglutination is used to determine the titre of immunoglobulin M (IgM), and the indirect antiglobulin technique is used to determine the titre of immunoglobulin G (IgG). We consider a titre of 1 : 250 to be critical. We do not permanently exclude donors with titres above the critical level, and we do not prefer donors of blood group A or B over donors of blood group O.

c) We attempt to resolve the problem by reducing the volume of plasma.

d) The plasma is replaced by platelet additive solution.

e) When apheresis blood group O platelets are considered issued to an A/B blood group recipient, plasma from several platelet units is diluted 1 : 250 and tested for IgM and IgG. If no antibody is detected at this dilution, the platelet units are issued. If antibody is detected in a unit which has to be transfused (i.e. HLA- or HPA-matched unit) the platelets are centrifuged and resuspended in platelet additive solution shortly before transfusion.

Question 4

In Norway we use ABO-compatible platelets for all patients, with the exception of blood group A_2-platelets that are considered clinically compatible also to patients who are not blood group A. In selected patients HLA- or HPA-compatibility is preferred over ABO-compatibility.

Bjarte G. Solheim
Rikshospitalet University Hospital
University of Oslo
NO-0027 Oslo
Norway
E-mail: bjarte.solheim@rikshospitalet.no

B. Zupanska

Question 1

I have not seen cases of haemolysis after transfusion of platelets.

Question 2
As a rule, we transfuse platelets from ABO-identical donors. Regarding the patients who require human leucocyte antigen (HLA)- or human platelet antigen (HPA)-matched platelets, see the answer to question 3.

Question 3
We do not determine the titre of anti-A/B in donors, because we transfuse platelets from ABO-identical donors.

For patients refractory to platelet transfusions and with HLA antibodies, we select compatible platelets (by cross-matching with lymphocytes and sometimes also with platelets) from ABO-identical donors. Very rarely do we select HLA-matched/partly matched platelets or platelets without the antigen against which the antibody is suspected to be or really is directed. We try to find an ABO-compatible donor. If we have to give ABO-incompatible platelets, we remove/reduce the volume of the donor plasma and replace it with AB plasma or with plasma of a donor which does not contain antibodies against the recipient's A or B antigens. We do not replace the plasma by platelet additive solution because this has not yet been registered in our country.

To date we have transfused HPA-matched platelets, found in our registry, to five patients with antibodies to HPA, refractory to random platelets. All of these patients were ABO compatible.

Question 4
As mentioned above, we use ABO-compatible platelets for almost all patients. If we have to give incompatible platelets, we choose 0-group platelets resuspended in AB group plasma.

Barbara Zupanska
Institute of Haematology and Blood Transfusion
5 Chocimska Str. 00957 Warsaw
E-mail: zupanska@ihit.waw.pl

M. Lozano, J. Cid & R. Mazzara

Question 1
No, we have not seen cases of haemolysis after transfusion of platelets.

Question 2
Some time ago in our centre we implemented preventive measures to avoid haemolysis caused by ABO-mismatched platelet concentrate (PC) transfusion, a fact that could explain why we have not seen any cases of haemolysis in recent years.

Question 3
To prevent haemolysis in recipients caused by a minor ABO-mismatched apheresis product, for a volume higher than 150 ml we reduce the plasma volume by centrifugation [1] immediately before transfusion, yielding a final volume of ≈ 90 ml.

For pooled PCs, before using a platelet additive solution, we applied the same strategy as in apheresis products. Currently, with leucoreduced pooled buffy coat-derived PC in additive solution with a plasma carryover of ≈ 30%, we no longer take the plasma ABO group into account.

Question 4
We try to transfuse ABO group identical PC whenever possible for all patients. When this goal cannot be accomplished, our priority is to avoid or significantly reduce the infusion of ABO-incompatible plasma to the recipient while maintaining compatibility between ABH platelet antigens and recipient isohaemagglutinins [2].

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Miguel Lozano
Roberto Mazzara
Department of Hemotherapy and Hemostasis
Agustí Pi i Sunyer Biomedical Research Institute (IDIBAPS)
Hospital Clínic
University of Barcelona
Villarroel 170
08036 Barcelona
Spain
E-mail: mlozano@clinic.ub.es

Joan Cid (present address)
Blood Transfusion Center and Tissue Bank
Barcelona
Spain

F. Knutson & R. Norda

Question 1
No incidents of haemolysis after transfusion of apheresis platelets or of pooled concentrates have been reported to the Swedish haemovigilance system.

Question 2
Measures are taken to prevent haemolysis, caused by anti-A/B in platelet concentrates, in the recipients of apheresis platelets. However, if human leucocyte antigen (HLA)- or human platelet antigen (HPA)-matched platelets are required, that is our first concern.

Question 3
a) No, we do not transfuse platelets only from ABO-identical donors.

b) All our apheresis platelet donors with blood type O are checked for anti-A/B and for HLA antibodies. Titration of anti-A/B immunoglobulin M (IgM) and immunoglobulin G (IgG) is performed by using the tube-technique [1]. Critical titres are believed to be 1 : 100 for IgM and 1 : 400 for IgG. We do not permanently exclude donors with titres above the citical level. A low titre of both IgG and IgM means acceptance as a universal donor, whereas a high titre of one or both means acceptance as a donor for a recipient of the same ABO type. We have no preference with respect to ABO-type. The majority of our donors are low-titre donors with blood type O and the rest are of blood type A.

c) No, we don't resolve the problem by reducing the volume of plasma.

d) We are planning to replace the plasma with an additive solution for quality reasons.

e) No other measures are used or planned.

Question 4

We use ABO-compatible platelets for all patients.

Reference

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Folke Knutson
Clinical Immunology and Transfusion Medicine
University Hospital
SE-751 85 Uppsala
Sweden
E-mail: Folke.Knutson@akademiska.se

Rut Norda
Clinical Immunology and Transfusion Medicine
University Hospital
SE-751 85 Uppsala
Sweden
E-mail: Rut.Norda@akademiska.se

B. M. Frey

The Zürich Blood Transfusion Service of the Swiss Red Cross is the largest Regional Transfusion Service of the country regarding production and distribution of platelet concentrates (PC). Annually, we produce and deliver more than 5500 units to about 65 hospitals and transfusion services. Since years, we provide about 80% single donor apheresis units (SDPC) and 20% pooled buffy coat units (BCPC). As a responsible Medical Director and CEO of the Zürich Blood Transfusion Service, I am delighted to be able to contribute to this International Forum.

Question 1

Annually, the Zürich Blood Transfusion Service delivers about 4500 units of platelet concentrates (80% single donor platelet concentrates (SDPC), 20% pooled buffy coat platelet concentrates (BCPC) to 61 hospitals and transfusion services. We are not aware of any case of hemolysis due to platelet transfusion across minor ABO incompatibility. However, we are not directly involved in the administration of products to patients and therefore might miss clinical outcome information.

Question 2

Yes. In collaboration with the clinicians, we select the PCs for transfusion according to the ABO group of recipient. However, for logistical reasons, we provide only PCs of group A and O. Therefore, ABO-mismatched transfusions of PC will occur in many cases.

Question 3

Each donor of an SDPC is tested for the presence of anti-A and anti-B hemolysins. If the titre is > 1 : 16, the product will be labelled and used for ABO-matched receipients only.

For BCPC the plasma will be replaced by platelet additive solution. Therefore, these products are not tested for hemolysins.

Technically, the hemolysins are determined by using test cells of type A1 and B. We use a microtiter plate format (96-well plate) and measure the haemolytic reaction photometrically.

There is no policy to defer hemolysin-positive donors from apheresis donation. However, for every apheresis donation the donor will be retested for hemolysins and the product will be labelled accordingly.

Question 4

ABO-compatible PCs will be delivered according to the transfusionist's request. However, we believe that ABO-compatible PCs are mainly indicated in cases needing prophylactic or chronic platelet substitution or carrying antibodies to human leucocyte antigens (anti-HLA) or to human platelet antigens (anti-HPA). For therapeutic use, ABO-minor-mismatched PCs without significant amount of isohemolysins seem to work well.

Beat M. Frey
Zürich Blood Transfusion Service
Hirschengraben 60
CH-8001 Zürich
Switzerland
E-mail: bm.frey@zhbsd.ch

S. MacLennan

Question 1

The 2003 Serious Hazards of Transfusion (SHOT) survey reported two incidents of significant haemolysis caused by apheresis platelets, both of which were from hospitals served by the National Blood Service (NBS) [1]. One incident concerned a 3-month-old infant postcardiac surgery, who

was given multiple transfusions of O Rhesus D-negative platelets owing to a shortage of A Rhesus D-negative neonatal platelets. Although the donations were tested and found to be negative for high-titre anti-A/B, it is possible that the haemolysis occurred as a result of repeated transfusion. The other incident involved a 31-year-old man, who was transfused with Group O platelets. Retrospective testing of the donor demonstrated high titres of both immunoglobulin G (IgG) and immunoglobulin M (IgM) anti-A.

In the previous 5 years of SHOT reports, a total of six haemolytic reactions to platelet transfusion were reported [2].

Question 2

Yes, the NBS has a national protocol for testing all donations (not just apheresis platelets) routinely for the presence of anti-A/B.

Question 3

a) The NBS has drawn up a clinical policy entitled 'ABO and Rh D compatibility in relation to platelet transfusion' (available on the NBS website: www.blood.co.uk/hospitals/guidelines/index.hm) [3]. This recommends transfusing ABO-identical platelets whenever possible, but recognizes that this is not always possible owing to additional special requirements, e.g. gamma-irradiated, cytomegalovirus (CMV)-seronegative, or shortages of a group. If a group A platelet is requested and not available, then a group B platelet is offered in preference to group O, and vice versa. If incompatible platelets are being transfused, then they should be labelled 'high-titre negative' (HT neg; see below).

b) A national procedure for high-titre testing has been in place in the NBS for several years. Until very recently the method used was an inhibition method, which used AB substance to neutralize IgM in most samples, and those that then still agglutinated cells were considered 'high titre'. This test identified ≈ 5–10% of donations as 'high titre' and these were directed for use in patients of the compatible group only. This method has now been withdrawn because AB substance as a reagent is no longer available, and a new method has been implemented.

The new method is performed on the Olympus PK7200, on all donations, in parallel with routine donation testing. All steps are fully automated and tested on the Olympus microplates. Fifteen microlitres of a 1 : 20 dilution of donor plasma in phosphate-buffered saline is added to 25 µl of A_2B cells. The detection of any agglutinated red cells is a positive result. A negative result is recorded when there is no agglutination, and these donations are labelled as 'HT neg'. Positive donations are not specifically labelled. This means that if a hospital blood bank knows that ABO-incompatible platelets are being given, it can select a donation labelled as 'HT neg'. This applies to pooled platelets (all of the contributing donations must test HT neg to have the final component labelled as such) as well as apheresis platelets.

This technique nationally has been found to give an overall reactive rate of 10%.

A further initiative with regard to high-titre testing is being taken forward by the Standing Advisory Committee on Immunohaematology for the UK Blood Transfusion Services. It is developing two standard reagents (positive control and negative control) for use by the UK Blood Services for assessing the cut-off of their testing methods. The controls are designed to detect anti-A/B, with a cut-off of 1 : 128, by using the manual tube technique.

Donors found to be HT positive are not specifically excluded from the panel, but their donations are not selected for transfusion to patients of incompatible groups. In addition, these donations are not used for manufacturing any neonatal components.

The majority of platelet apheresis donors in the NBS are group O or group A. Recruitment has not been targeted specifically for A and B donors in preference to those of group O. Hospitals are advised that group O platelets with high titres of anti-A or anti-B should be transfused only to group O recipients.

c) Plasma reduction of platelet components is not currently employed.

d) It is planned to implement the use of platelet additive solution routinely during the next year. This may offer advantages for both TRALI and variant Creutzfeldt–Jacob disease (vCJD) risk reduction in addition to reducing the anti-A/B content.

Question 4

As outlined above, ABO-compatible platelets are used whenever possible. We do not routinely measure the titre of anti-A/B in patients, including bone marrow transplant recipients.

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Sheila MacLennan
National Blood Service
Bridle Path
Leeds, LS15 7TW
UK
E-mail: sheila.maclennan@nbs.nhs.uk

J. M. Heal & N. Blumberg

Question 1

We have not seen clinically evident cases of haemolysis after transfusion of incompatible platelets in recent years, as > 90% of our platelet transfusions are ABO identical and we only rarely administer group O platelets to non-O recipients, for the reasons discussed below. Prior to 1990, when we routinely administered ABO-mismatched platelets, we frequently observed patients with positive direct antiglobulin tests, increased red cell transfusion needs and other evidence of haemolysis.

Question 2

For unavoidable ABO-mismatched platelet transfusions, as in patients receiving human leucocyte antigen (HLA)- or human platelet antigen (HPA)-matched platelets, we wash before transfusing to remove the incompatible supernatant plasma antigen and antibody. While some might consider this plasma reduction to be unnecessary, we are increasingly convinced that the administration of large quantities of incompatible anti-A and anti-B, or soluble A and B antigens, may have deleterious effects on many patients that are not obvious [1].

Some clinical events that we hypothesize are caused by the transfusion of ABO-incompatible plasma and cells are not as easily attributable to the transfusion as post-transfusion haemolysis. For example, the transfusion of ABO-mismatched platelets increases the risk of HLA alloimmunization and platelet refractoriness in the two small randomized trials addressing this issue [2,3]. Transfusion of incompatible plasma leads to large quantities of circulating high-molecular-weight, long-lived immune complexes. These immune complexes fix complement, bind to platelets, leading to phagocytosis by monocytes, and carry unknown potential for morbidity [4]. Such morbidity speculatively could include interference with anti-leukemia cellular immunity [5] or a pro-inflammatory predisposition to multi-organ failure and death in cardiac surgery [6].

The assumption that the sole biological and clinical effect of transfused anti-A and anti-B is to cause destruction of circulating red cells seems improbable to us. ABH antigens are present in the recipient in soluble form, on endothelial cells, white cells and virtually every other cell in the body. Transfusion of incompatible soluble A and B antigens may likewise not be benign.

Question 3

We attempt to transfuse only ABO-identical platelets, particularly to patients receiving repeated platelet transfusions. When non-ABO identical platelets must be administered owing to shortages or changing ABO blood groups in allogeneic stem cell transplant recipients, we routinely transfuse saline-resuspended, machine-washed O platelets preferentially. There are minimal quantities of incompatible cells, soluble antigen and antibody in this transfused component. We also sometimes decrease the number of transfused whole-blood platelet concentrates from a routine pool of five units to three or four, so that only ABO-identical transfusions are administered.

We do not use titres to select mismatched platelets because we believe that this method is unreliable at predicting biological and clinical effects in the recipient. We are concerned that employing titres of incompatible ABO antibodies to select 'safe' donors may represent treating ourselves rather than effectively treating the patient, given the lack of data supporting the predictive value of titres.

Question 4

We are of the opinion that the use of the term 'compatible', derived from red cell transfusions that are relatively plasma poor, should not be applied to platelet transfusions that contain an order of magnitude greater amounts of plasma-soluble antigen and antibody. Platelet transfusions are more analogous to whole-blood transfusions in this regard, and in the modern era, ABO non-identical whole blood would rarely or never be considered suitable for transfusion. Unless plasma reduced, we believe that platelet transfusions should ideally be ABO identical.

In our centre, thrombocytopenic patients with haematological diseases are transfused solely with ABO-identical or washed platelet antigen and antibody-identical platelet concentrates. We administer a reduced dose of whole blood-derived platelet concentrates (e.g. a pool of four rather than of five), rather than give incompatible plasma or platelets to the patient. We also transfuse solely ABO-identical platelets to patients with ventricular assist devices who are awaiting cardiac transplantation, because their platelet transfusion needs are considerable over a period of days to weeks, somewhat analogous to patients with haematological diseases.

For all other patients we attempt to give only ABO-identical platelets, but occasionally no such platelets are available. Under these circumstances we will transfuse unwashed ABO-mismatched platelets. This happens most commonly in emergency transfusions for massive haemorrhage in trauma or liver transplantation, where there is no time for washing or plasma reduction by centrifugation. The incidence of this is fewer than 5–10% of transfusions in our institution.

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Joanna M. Heal
Associate Clinical Professor of Medicine
Hematology-Oncology Unit
Department of Medicine
University of Rochester
Rochester
NY 14642
USA
E-mail: jmheal@aol.com

Neil Blumberg
Transfusion Medicine
University of Rochester
Box 608
Rochester
NY 14642
USA
E-mail: neil_Blumberg@urmc.rochester.edu