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ABO-Incompatible Kidney Transplantation

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1. Introduction

ABO antigens are composed of sugar chains and exist not only on red cells but also on many other cells including endothelial cells and epithelial cells of various organs such as kidney, heart, bowel, lung, and pancreas (Marionneau et al., 2001). ABO antibodies, which have been called as isoagglutinins, are preformed antibodies directed against missing A or B antigens. The source of anti-A/B antibodies is thought to be gastrointestinal and environmental bacteria, such as the enterobacteriaceae, which possess ABO-like structures on their lipopolysaccharide coats (Yamamoto, 2004). These preformed ABO antibodies are clinically important in transfusion and organ transplantation medicine because they can cause acute hemolytic transfusion reaction in ABO-incompatible (ABO-I) blood transfusion and hyperacute rejection in ABO-I organ transplantation.

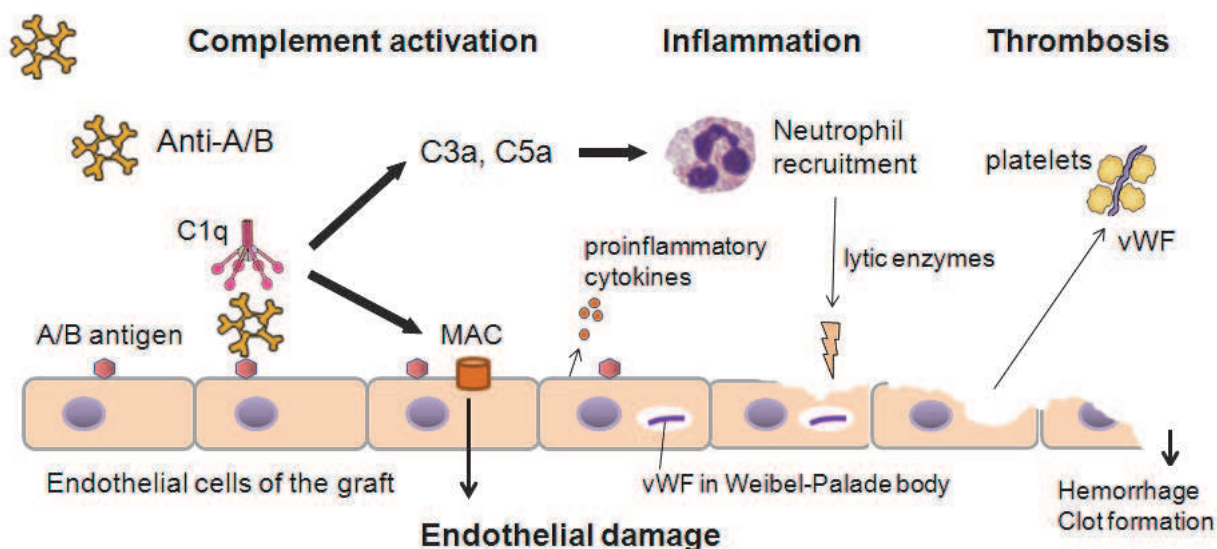


Fig. 1. Proposed mechanism of hyperacute rejection in ABO-incompatible organ transplantation.

Hyperacute rejection is induced by the binding of anti-A/B to antigens expressed on the endothelial cells of the ABO-I graft and activation of complement system (Fig. 1). Subsequently, endothelial damage, inflammation and platelet aggregation can be provoked, leading to vascular thrombosis, occlusion of blood supply and rejection.

ABO-I kidney transplantations were first reported in late 1950s and early 1960s (Hume et al., 1955; Murray et al., 1960; Starzl et al., 1964; Kissmeyer-Nielsen et al., 1966). These early experiences showed that hyperacute rejection could occur, and therefore, crossing the ABO barrier was excluded in the field of kidney transplantation.

In 1981, Slapak et al. first introduced the concept of depleting anti-A/B antibodies when they used modified plasmapheresis and successfully overcame the major donor-recipient blood group incompatibility in kidney transplant patient. Later, the same group reported on pre-transplantation immunoadsorption and plasmapheresis for ABO-I kidney transplantation, showing a high survival rate of 87% (Slapak et al., 1990).

Another group also started a living donor ABO-I kidney transplantation program in 1982, after this group inadvertently experienced an ABO-I cadaver kidney transplantation due to an error in donor ABO typing. In spite of the A₁ to O major ABO-incompatibility, the kidney graft from ABO-I cadaver functioned well with a basic immunosuppressive regimen including a short course of polyclonal antibody with azathioprine, and has been reported to be still functioning 22 years later (Squifflet et al., 2004). In this group, plasmapheresis was chosen to remove antibodies before transplantation and to prevent the occurrence of antibody-mediated hyperacute rejection. In addition, the immunosuppressive regimen was started 3 days prior to transplantation, and splenectomy was performed on the day of transplantation (Alexandre et al., 1985a, 1985b, 1986). Although the transplantation was successful, the return and persistence of anti-donor blood-group antibody was observed in spite of chronic immunosuppression. However, even with the continued presence of these antibodies and the persistence of the target antigen in the kidney, most of the graft continued to function well (Alexandre et al., 1991; Cardella et al., 1987; Reding et al., 1987). It was suggested that ABO blood group incompatibility need not be an absolute barrier to successful kidney transplantation.

2. Accommodation

It has been observed that ABO-I kidney grafts functioned well without rejection in recipients having high titers of anti-A/B antibodies. This phenomenon has been termed accommodation and regarded as an acquired resistance of an organ to immune-mediated damage (Bach et al., 1997; Lynch & Platt, 2008, 2010; Platt et al., 1990). In accommodation state, the graft is not pathologically injured despite the presence of circulating anti-donor antibodies.

The mechanism of accommodation is yet to be elucidated. It was postulated that accommodation might be involved in change in antibodies, change in antigen, modified control of complement, or acquired resistance to injury (Lynch & Platt, 2008). Complement regulation was thought to be essential for the survival of transplants over time and thus for accommodation to be manifested. C4d deposition without signs or symptoms of rejection can be observed in accommodated kidney (Lynch & Platt, 2010). The occurrence of complement activation means that antibody binding is intact in accommodated kidneys, and the lack of lysis means that some regulatory pathways are working for graft survival in the accommodation.

Three possible outcomes of the binding of complement-fixing alloantibody to endothelial cells have been postulated (Colvin & Smith, 2005). Hyperacute or acute rejection can be resulted, if the complement is fully activated. Accommodation can be achieved, if complement activation is completely inhibited. Incomplete inhibition of complement might

be sufficient to prevent cell lysis but not to prevent complement activation, leading to endothelial cell activation and chronic antibody-mediated rejection (AMR).

Studies in mice showed that, in the absence of T-cell help, B cells that are exposed to incompatible carbohydrate antigens on allografts differentiate into cells that can produce non-complement-fixing antibody, and these B cells gradually become tolerant after prolonged exposure (Ogawa et al., 2004).

An acquired resistance to injury could reflect accommodation more comprehensively, but does not exclude other mechanisms. Actually, such resistance or protection could be appreciated, if some antibodies bind to graft and some complements are activated. Park et al. (2003) used microarrays, and compared five 1-year protocol ABO-compatible renal graft biopsies to four accommodated ABO-I graft biopsies. They identified significant alterations in gene expression in 440 probe sets, including SMADs, protein tyrosine kinases, TNF-alpha and Mucin 1. They concluded that accommodation is always present in well-functioning, long-surviving ABO-I kidney transplants. Regarding this self-protection against antibody-mediated damage, several novel mechanisms were suggested including the disruption of normal signal transduction, attenuation of cellular adhesion, and the prevention of apoptosis.

Accommodation is regarded as a good response to transplantation. It prevents acute antibody-mediated injury, thus allowing chronic process to ensue over time. Accommodation can be induced when antibodies that would cause rejection of a graft are removed from a recipient and then later return. In addition to this induced type, accommodation can occur spontaneously, without depleting antibodies. In this regard, the prevalence of accommodation would be higher than expected, and spontaneous accommodation may be the most common outcome of clinical organ transplantation (Tang & Platt, 2007). Accommodation still remains an evolving concept, and has a mixed support from experimental and clinical findings. The most important unanswered questions are how often and by which mechanisms accommodation occurs (Lynch & Platt, 2010). Accumulation of clinical evidences and research data would bring progress in understanding the biological implications of accommodation.

3. Current practice

The earlier works in the early 1980s were expanded greatly in Japan, where ABO-I kidney transplantation has been performed in more than 1,000 patients since 1989, and recently accounts for about 18% of all living donor kidney transplants (Takahashi, 2007). Later, a number of centers in USA and Europe have begun ABO-I kidney transplantations using similar protocols (Crew & Ratner, 2010).

The clinical outcome of ABO-I kidney transplantation improved remarkably in the last 10-15 years since the routine use of tacrolimus and mycophenolate. Clinical literatures repeatedly showed that ABO-I kidney transplantation has outcomes comparable to ABO-compatible kidney transplantation (Haidinger et al., 2009; Jeon et al., 2010; Kenmochi et al., 2008; Oetl et al., 2009; Thielke et al., 2007). One-year and five-year survival rates of ABO-I kidney transplants showed little difference from those of ABO-compatible kidney transplants, and their renal functions based on creatinine levels also showed no difference. Recently, the Japanese data on 851 ABO-I kidney transplantations was summarized (Tanabe, 2007a). According to this report, 1-, 3-, 5-, and 10-year patient survivals have been 95%, 92%, 90%, and 85%, respectively, whereas 1-, 3-, 5-, and 10-year graft survivals have been 89%, 85%,

79%, and 61%, respectively. These improved outcomes are attributed to a clearer understanding of the mechanisms underlying accommodation and acute AMR, permitting the development of new therapeutic strategies. There were significant differences in graft survival and the incidence of rejection before and after the introduction of tacrolimus/mycophenolate mofetil.

3.1 Induction therapies

Initial protocols for ABO-I kidney transplantation included splenectomy, which was performed in most recipients until 2004. Recently, a monoclonal antibody directed against CD20 on B cells, rituximab, has replaced splenectomy in most centers (Fig. 2). The use of rituximab eliminated the need for additional surgical intervention, and the outcomes with rituximab infusion alone were equal to those with splenectomy, providing more evidence that splenectomy is unnecessary (Crew & Ratner, 2010; Tanabe et al., 2009).

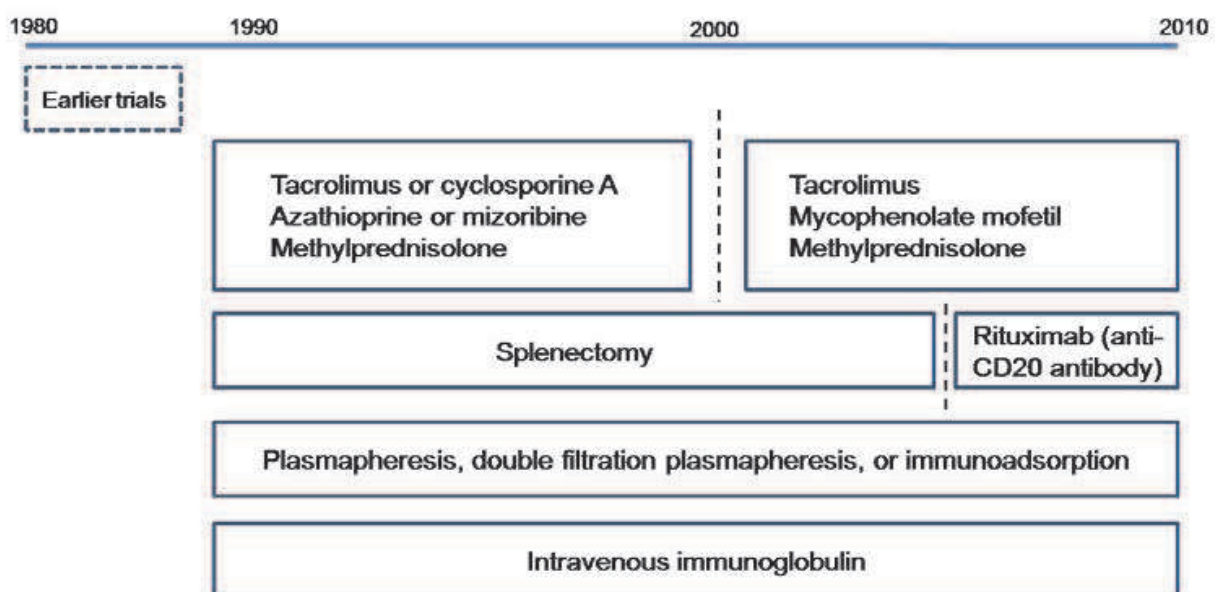


Fig. 2. Changes of preconditioning protocols for ABO-incompatible kidney transplantation. Between 1989 and 1999, a triplicate immunosuppressive regimen consisted of tacrolimus or cyclosporine A plus azathioprine or mizoribine plus methylprednisolone. Since 2000, tacrolimus, mycophenolate mofetil, and methylprednisolone have been used. Splenectomy was performed until 2004, and recently anti-CD20 antibody (rituximab) became an alternative to splenectomy. In most cases, 3-7 sessions of plasmapheresis or immunoadsorption have been performed before transplantation.

Rituximab as an alternative to splenectomy markedly reduced the incidence of AMR and greatly improved the results, becoming a clinically proven effective regimen for a successful ABO-I kidney transplantation. Interestingly, one recent study reported excellent outcomes without splenectomy or rituximab, questioning whether rituximab is indeed necessary (Segev et al., 2005). The authors suggested that rapid allograft accommodation may limit the need for long-term antibody suppression provided by splenectomy or anti-CD20, thereby eliminating the added infectious risk of these modalities and removing another disincentive to ABO-I transplantation.

Before 2000, a triplicate immunosuppressive regimen consisting of tacrolimus or cyclosporine A plus azathioprine or mizoribine plus methylprednisolone was mainly used. Thereafter, tacrolimus, mycophenolate mofetil, and methylprednisolone were used at most institutions. A greater incidence of acute rejection that was observed during the cyclosporine A era was markedly reduced in the tacrolimus era. In particular, the routine use of tacrolimus and mycophenolate mofetil significantly reduced acute rejection rates in patients with high-pretransplant isoagglutinin titers, and improved their outcomes to the levels comparable to those with low titers (Ishida et al., 2007).

3.2 Antibody reduction therapies

In all protocols, plasmapheresis to reduce and control anti-A or -B titers is a central feature. In most cases, ABO-I kidney transplantation recipients underwent 3-7 sessions of plasmapheresis (therapeutic plasma exchange) or double-filtration plasmapheresis before transplantation to reduce isoagglutinin titers. Plasmapheresis effectively removes anti-ABO antibodies, and approximately 20% of reduction is expected in each treatment. Its side effects, which are observed in approximately 5% of patients, are mainly hypocalcemia and pruritus/urticaria, and are usually mild and well tolerated (Tobian et al., 2008, 2009).

Plasmapheresis removes not only ABO antibodies but also the other protective antibodies or clotting factors, potentially increasing the risk of perioperative infection or bleeding. In contrast to plasmapheresis, immunoadsorption method can selectively remove anti-ABO antibodies, unaffected the levels of the other plasma proteins. The blood type-specific columns can effectively remove anti-A or anti-B antibodies, and approximately 30% of anti-A/B IgM and 20% of anti-A/B IgG levels can be removed after a single treatment (Valli et al., 2009). In spite of its physiologic technique and successful clinical applications, the high cost of immunoadsorption column is a major limiting factor blocking its widespread use. The absence of randomized trials, which compared plasmapheresis and immunoadsorption, makes precise comparison of cost and outcomes impossible at the current point.

Plasmapheresis is a form of therapy to separate plasma from a person's circulating blood, removing pathogenic substances in plasma, and returning the remainder to the patient, usually with replacement fluids. The removal of a pathologic substance is affected by its concentration in circulating blood, the processing volume of blood and the degree of intravascular distribution. For example, IgM or fibrinogen are efficiently removed due to their predominantly intravascular distribution compared to IgG, which is predominantly extravascular. The alteration of immunoglobulin after single-plasma volume exchange was reported as about 63% decrease from baseline (Orlin & Berkman, 1980). An example of the changes of anti-A and anti-B antibody titers and creatinine levels before and after ABO-I kidney transplantation is shown in Fig. 3 (Moon et al., 2009). Efficiency of antibody removal is variable according to the patients. It is important that recipients or potential recipients of ABO-I kidneys should receive plasma that contains no ABO antibody against the graft for transfusion or plasmapheresis.

Plasmapheresis is indicated in various diseases such as thrombotic thrombocytopenic purpura, myasthenia gravis, or hyperviscosity in monoclonal gammopathy. Regarding indication for plasmapheresis, The American Society for Apheresis (ASFA) has published the guidelines and recommendations (Szczepiorkowski et al., 2010). According to this ASFA guideline, ABO-I kidney transplantation is classified as category II, in which plasmapheresis is generally accepted but considered to be supportive or adjunctive to other, more definite treatments, rather than a primary first-line therapy.

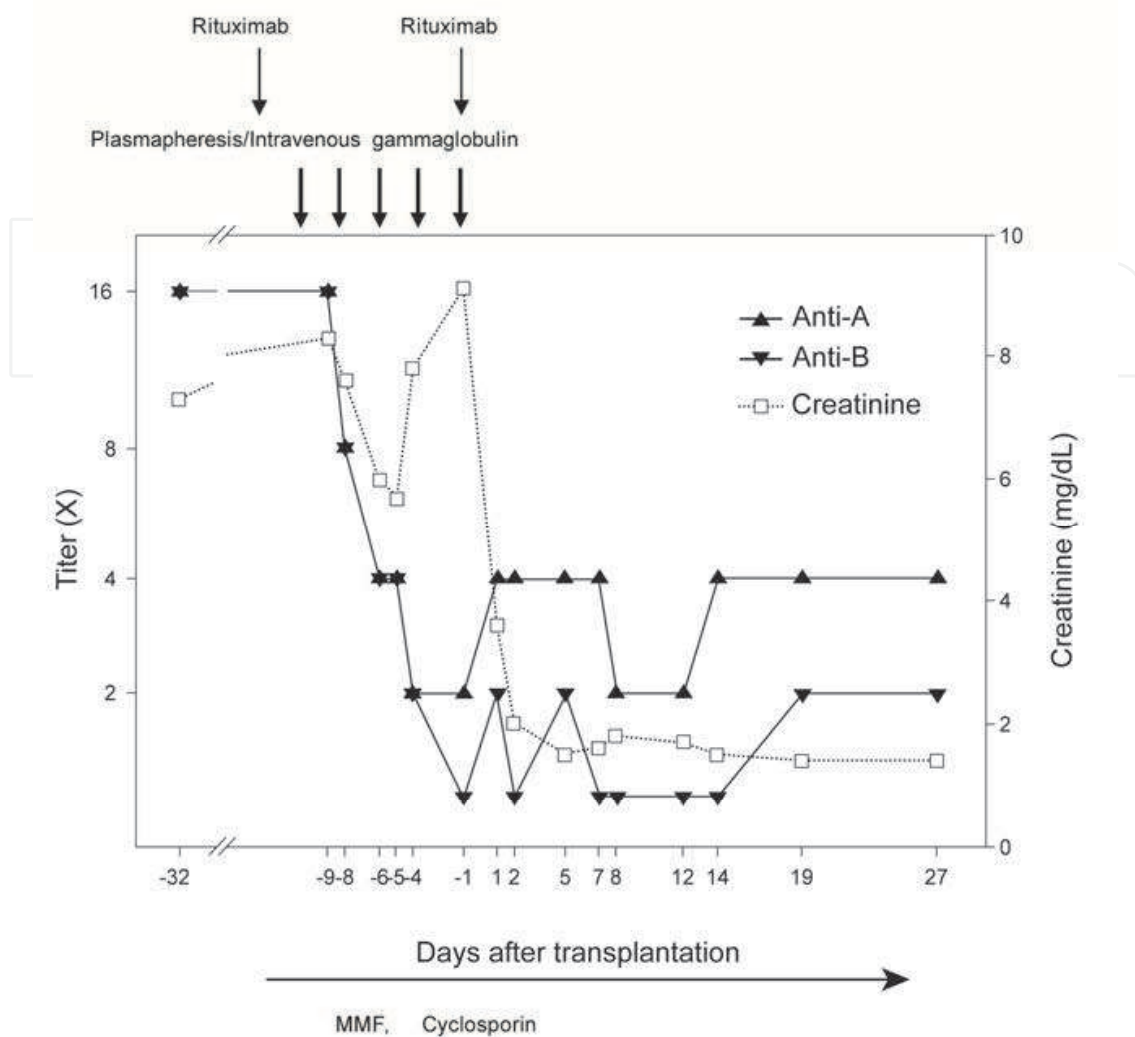


Fig. 3. An example of the changes of anti-A/anti-B antibody titers and creatinine levels before and after ABO-incompatible kidney transplantation. The patient's blood type was O, Rh+ and the donor's blood type was B, Rh+. A combination therapy with plasmapheresis, intravenous gammaglobulin, rituximab and potent immunosuppression was performed. Although the patient's baseline anti-A and anti-B titers were relatively low (1:16 for both anti-A and anti-B), titers were successfully decreased after each plasmapheresis procedure (average 1 fold), finally decreased to 1:1. The kidney transplantation was successful without any sign of hyperacute or acute rejection (modified from the refernece by Moon, et al (2009) with permission of Korean Journal of Laboratory Medicine).

Generally, plasmapheresis is performed using automated instruments. These instruments have specialized devices for blood withdrawal, anticoagulation, separation, return of blood, replacement and discard or collection of separated substances. The separation process is performed by centrifugation or filtration. In centrifugation method, blood components are separated by specific gravity and divided as plasma, platelets, leukocytes and red blood cells. In filtration method, blood is passed through a filter, and blood components are separated by their differences in particle size. Filtration and centrifugation can be combined by using rotating filter.

In conventional plasmapheresis, smaller proteins such as albumin are also removed in addition to pathogenic molecules, antibody or high molecular weight proteins. In general, plasma separated with a plasma separator is discarded and replaced with the same volume of replacement fluid such as fresh frozen plasma or albumin solution. There are several options of plasmapheresis, which separate blood components more selectively.

Double filtration plasmapheresis (DFPP) uses two filters which have different pore sizes. In the first filter, blood is separated as plasma and cell components, and plasma is further separated by the second filter. Large molecular-weight proteins including immunoglobulins such as anti-donor isoagglutinins are removed, while smaller molecular-weight substances such as albumin are returned to the patient's circulation. In this procedure, need of replacement is decreased compared with conventional plasmapheresis, thus adverse effects related to the replacement fluid can be reduced (Fig. 4) (Genberg et al., 2010; Tanabe, 2007b). In the immunoadsorption, specialized adsorption column selectively adsorbs a specific substance such as immunoglobulin or low-density lipoprotein. This process removes the element of interest specifically and the remaining elements are returned to the patients. Many kinds of immunoadsorption devices for the removal of various types of components are commercially available but generally expensive. For the removal of anti-A and -B antibody, AB antigen-specific carbohydrate columns (Glycosorb AB, Glycorex Transplantation AB, Lund, Sweden) were developed (Tyden et al., 2005) and have been widely used in more than 400 cases of ABO-I kidney transplantation (Genberg et al., 2010; Tyden et al., 2005; Winters et al., 2004). This procedure could decrease the complications associated with plasma exchange such as coagulopathy and transfusion reactions.

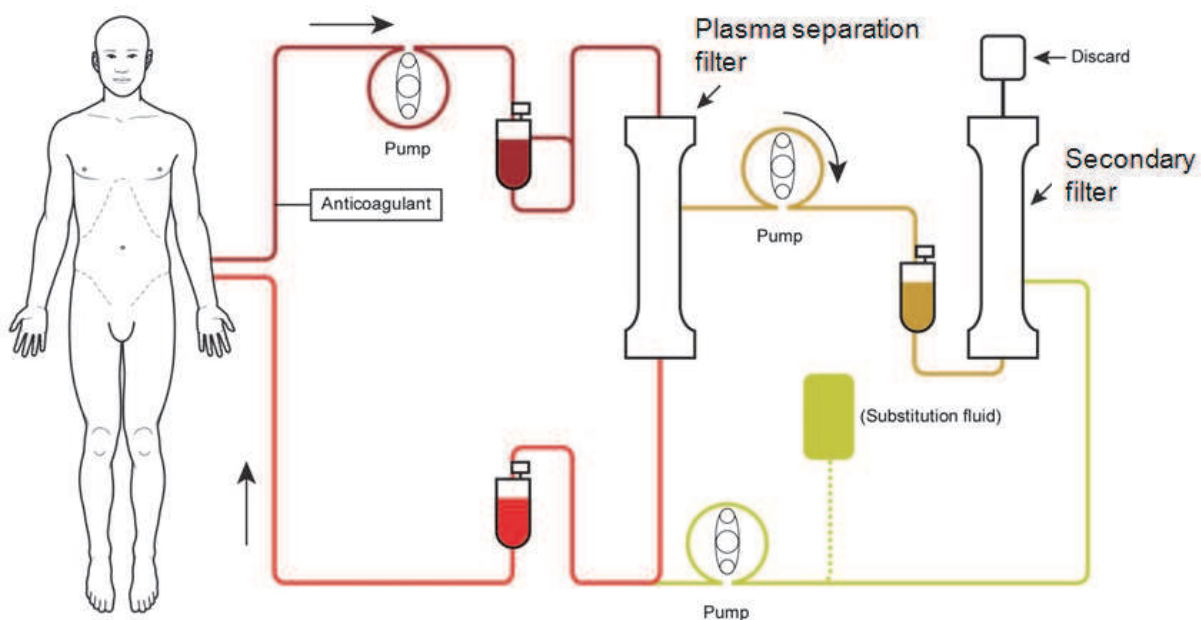


Fig. 4. Schematic presentation of double filtration plasmapheresis (DFPP). In DFPP, plasma separated with a plasma separator (1st filter) passes through the plasma component separator with a small pore size (2nd filter). Molecules that are larger than the pore size such as immunoglobulins are removed, and smaller molecules such as albumin are returned to the patient.

4. Determination of isoagglutinin titer

To reduce isoagglutinin titers prior to ABO-I kidney transplantation, preparative regimens including plasmapheresis, DFPP, or immunoadsorption and immunosuppressive therapy have been used. The clinical significance of isoagglutinin titer in ABO-I kidney transplantation is not entirely clear (Tobian et al., 2011). The goal of isoagglutinin titer to prevent hyperacute rejection is variable across transplantation centers, ranging from $\leq 1:8$ to $\leq 1:32$ before transplantation (Crew & Ratner, 2010). However, minimal research has been performed to determine the optimal pretransplant titer. The possibility of AMR would decrease as anti-donor antibody titer decreases. In our institution, the titer is lowered to $\leq 1:4$ before transplantation. The measurement of isoagglutinin is known to be essential in the assessment of the efficacy of antibody removal, and the prediction of AMR (Kobayashi & Saito, 2006). Although most recipients with AMR had an elevated titer, the positive predictive value of a high titer for AMR was poor (Tobian et al., 2010). Thus, posttransplant titers should be monitored, but must be combined with the other factors assessing AMR.

Accurate measurement of isoagglutinin titer is an important aspect for successful ABO-I kidney transplantation. If the isoagglutinin titer is underestimated compared to the actual titer of patient, we could consider a patient as safe for transplantation and it could lead to rejection or short duration of allograft survival (Crew & Ratner, 2010). IgM antibody mediates complement activation and endothelial damage in AMR, and it is more rapidly removed by plasmapheresis than IgG. However, IgG titers are more emphasized for patient eligibility, rejection risk, and plasmapheresis guidance. Reporting both IgM and IgG titers has been recommended by a working group from US centers (Montgomery et al., 2004). Importantly, measured titers are method-dependent and considerably variable according to assays.

	Tube method	Column agglutination	Flow cytometry
A column ingredient	Not needed	Sephadex gel or glass bead	Not needed
Use of RBC	Yes	Yes	Yes
Antihuman globulin	Yes	Yes	No
Secondary antibody	No	No	Yes
Deletion of IgM	DTT or 2ME	DTT or 2ME	Not needed
Interpretation	Agglutination	Agglutination	Fluorescence detection
Result	Titer	Titer	MFIR or titer
Instrument	Not needed	Not needed	Needed
Cost	Low	Intermediate	Relatively high
Assay time	30 - 60 min	30 - 60 min	1- 2 hours

DTT, dithiothreitol; 2ME, 2-mercaptoethanol; MFIR, mean fluorescence intensity ratio.

Table 1. Various assays for measurement of isoagglutinin titer

There are several options for the measurement of isoagglutinin titers: conventional tube method, gel or bead column agglutination method, and flow cytometry (Krishnan et al., 2008; Stussi et al., 2005). These three methods are summarized in Table 1. In addition, enzyme-linked immunosorbent assay technique (Lindberg et al., 2011; Rieben et al., 1991), surface plasmon resonance (Kimura et al., 2005; Yurugi et al., 2007), and KODE technology (Frame et al., 2007) were developed, although these methods are not routinely available in most institutions.

4.1 Conventional tube method

The conventional tube method has been used in most institutions for the semiquantitative measurement of isoagglutinin titers. IgG and IgM can be measured together, and if dithiothreitol or antiglobulin reagents are used, they can be measured separately. In general, recipient serum is serially diluted and incubated with RBC aliquots of the appropriate blood type in a test tube for about 10 minutes at room temperature. After the mixture is centrifuged, macroscopic agglutinations of RBCs are checked for IgM detection. For IgG detection, additional testing with antihuman globulin is performed to check the agglutination. Titers are determined as the highest dilution that produces 1+ macroscopic agglutination. However, technical variables greatly affect the results, and care should be taken to achieve the most uniform practice (Roback, 2008). Considerable inter-examiner variability may occur, because the titer is determined mainly by visual observation of agglutinated RBCs in tubes. Inter-institutional difference can also occur possibly due to variations in procedures and lack of assay standardizations.

A recent study reported the results of isoagglutinin titers from 26 different labs using sera from six patients of different blood groups (Kobayashi & Saito, 2006). In this report, inter-institutional variation between maximum and minimum value reached as much as 32-fold in IgM and 256-fold in IgG. These variations seemed to be due to different techniques between laboratories, but considerable variation was still noted after standardization of techniques. Another report also showed a large variation of isoagglutinin titers (a median three-fold difference) among three centers performing ABO-I kidney transplants in Germany and Sweden (Kumlien et al., 2007). In this report, gel hemagglutination technique significantly decreased inter-center difference (a median one titer difference) compared with tube methods.

4.2 Gel or bead column agglutination

In gel or bead column agglutination method, a cassette (or card) containing gels or beads is used. Commercially available assays include DiaMed ID Micro Typing system (Bio-Rad, Hercules, CA, USA), BioVue System (Ortho Clinical Diagnosis, Raritan, NJ, USA), or Olympus ID-Micro Typing System (Olympus Co., Tokyo, Japan). In these assays, plasma from the patient is stepwise diluted 1:2 with normal saline or phosphate buffered saline and packed RBCs are used to make a suspension with cell stabilization solution. In each incubation well, recommended cell suspension is mixed with diluted plasma. After incubation and centrifugation, agglutination is observed in card or cassette. In column agglutination method, negative (unagglutinated) test cells pellet to the bottom of the column, and positive (agglutinated) cells are captured at the top of or within the body of column (Fig. 5). The gel or bead particles trap the RBC agglutinates as a filter during centrifugation. The agglutination is graded from 0 to 4 +, and inverted value of the highest plasma dilution that gives a 1+ agglutination reaction is interpreted as the titer (Kumlien et al., 2007).

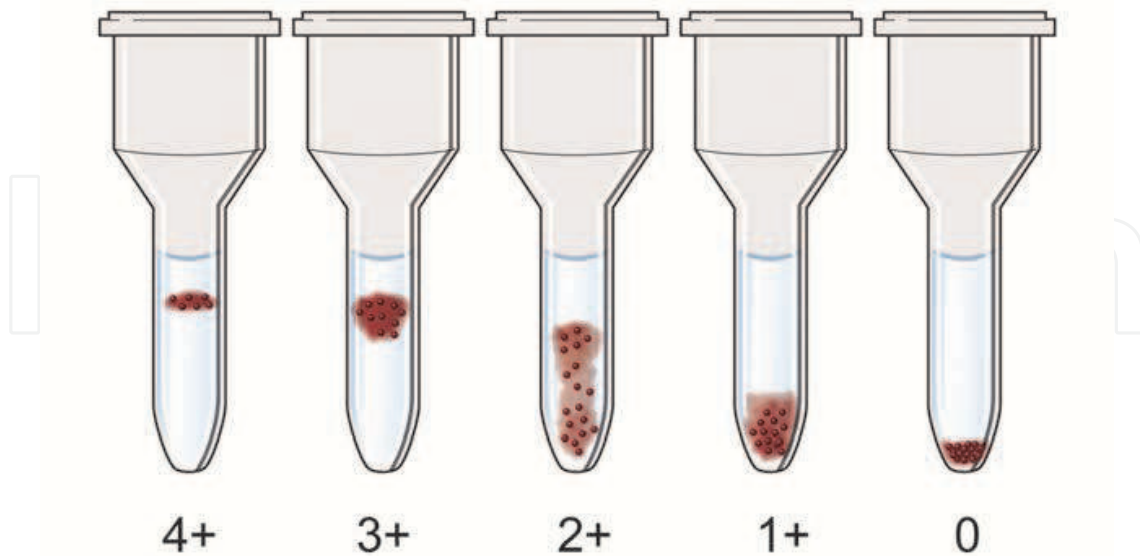


Fig. 5. Interpretation of column agglutination method. The agglutination is graded from 0 to 4+.

4.3 Flow cytometry

In flow cytometry method, quantifications of anti-A/B IgG and IgM are performed using fluorescence conjugated, anti-human IgG and IgM as secondary antibodies. A mixture of RBC suspension and recipient serum is transferred into the test tube and incubated (at 37°C in a CO₂ incubator for IgG antibody; and at room temperature, for IgM antibodies). After washing, fluorescence conjugated, anti-human IgG and IgM secondary antibodies are added in test tube. After incubation and washing steps, binding of anti-A/B antibody is measured by flow cytometry. Human AB serum, which is further depleted by incubation with highly concentrated A and B RBCs, can be used as a negative control, and human serum of blood group O is used as a positive control. Commercially available O RBCs with information of antigen expression are also helpful for the detection of irregular antibodies (Stussi et al., 2005).

Using undiluted serum, quantification of anti-A/B antibody can be determined by calculation of the geometric mean fluorescence intensity ratio (MFIR). This value is calculated by dividing the geometric mean fluorescence intensity of test sera with that of negative control. One study reported that the correlation coefficient between MFIR using flow cytometry and isoagglutinin titer was 0.870 for IgM and 0.783 for IgG (Stussi et al., 2005). For determination of titer using flow cytometry, recipient serum is serially diluted with normal saline solution (2% bovine serum albumin, 0.1% azide). After incubation and washing, secondary antibody is added. After reaction, binding of antibody is determined by flow cytometry. A gated value above assigned cut-off (5% for example) is regarded as positive serum dilution. In a study comparing the reproducibility of the results performed by various assays, flow cytometry showed excellent reproducibility and no measurement deviation was noted, whereas gel column agglutinin assay and tube technique showed two-fold and four-fold differences, respectively (Tanabe, 2007b). However, flow cytometry assay needs the flow cytometry instrument, and the reagents are relatively expensive.

5. Conclusion

The ABO blood group barrier is now being crossed in the field of transplantation, and ABO-I kidney transplantation is becoming more common worldwide. Removing the ABO barrier can expand the donor pool and increase the availability of organs for transplantation. Moreover, it can decrease the time on the organ waiting list, and eventually facilitate the timely transplantation before comorbid conditions develop in the patients. Currently observed long-term results of ABO-I kidney transplantation are similar to those of ABO-compatible kidney transplantation. With the application of adequate antibody reducing strategies, future results would be more promising. To promote accommodation and to prevent acute complement-mediated graft injury, methods for preventing and treating AMR are still needed. Researches for the insights into the mechanism of accommodation will provide us a scientific basis for the development of innovative approaches for the better outcome of ABO-I kidney transplantation.

As the number of ABO-I transplantation increases, there is a need of the optimal methods for ABO isoagglutinin titer for the effective monitoring of ABO-I transplanted patients. Compared with the conventional test tube method, gel card or flow cytometric measurement can provide more accurate and objective results. However, reproducibility, interpretation, and standardization of isoagglutinin titration methods are still unsatisfactory, and further researches should be performed to determine the optimal method for ABO antibody titer assessment. There are also several promising techniques under development, focused on the endothelium, enzymes, or blocking antibodies. Ongoing improvement of promising modalities could make more successful transplantation outcomes in this field.

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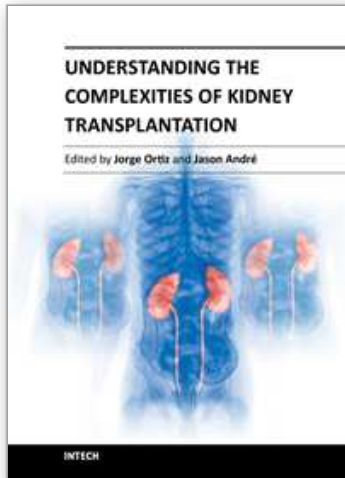
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Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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