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ABO incompatible kidney transplantation

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Table of Contents

Table of Contents.....	iii
Tables.....	iv
Executive Summary.....	1
HealthPACT Advisory.....	2
Introduction.....	3
Background.....	4
Description of the procedure.....	5
Intended purpose.....	8
Clinical need and burden of disease.....	8
Stage of development.....	9
Treatment Alternatives.....	10
Existing comparators.....	10
Clinical Outcomes.....	11
Safety.....	19
Effectiveness.....	20
Ongoing issues of ABOi transplantation.....	22
Potential Cost Impact.....	28
Ethical Considerations.....	30
Informed Consent.....	30
Training and Accreditation.....	31
Clinical Guidelines.....	31
Limitations of the Assessment.....	32
Search Strategy used for the Report.....	32
Availability and Level of Evidence.....	34
Sources of Further Information.....	35
Conclusions.....	36
Appendix A: Levels of Evidence.....	38
Appendix B: Profiles of studies.....	40
Appendix C: HTA internet sites.....	42
References.....	46

Tables

- Table 1:** Comparative studies investigating the safety and efficacy of ABOi kidney transplantation.
- Table 2:** Preoperative IgG antibody titre levels and corresponding graft survival rates (Group 1)
- Table 3:** Preoperative IgG antibody titre levels and corresponding graft survival rates (Group 2)
- Table 4:** Preoperative IgG antibody titre levels and corresponding incidence of acute humoral rejection
- Table 5:** Literature sources utilised in assessment
- Table 6:** Search terms utilised

Executive Summary

The average waiting time for kidney transplantation is four years. This highlights the severe disparity between the available donor kidney pool and the amount of end stage renal disease patients who require kidney transplantation to survive. Despite that fact that the medical community has attempted to alleviate this problem by educating the public on kidney donation, the shortage of donor kidneys continues to persist. At the time of writing, living kidney donations account for approximately 41% of total transplantation procedures. However, research has revealed that approximately 35% of living donors are rejected based on blood group incompatibilities alone. In an attempt to address this issue, researchers have investigated the viability of ABO incompatible (ABOi) kidney transplantation.

From the retrieved studies, there is some evidence that graft survival rates for ABOi recipients are comparable to ABO compatible (ABOc) recipients. However, three studies indicated that ABOi graft survival was significantly inferior to ABOc transplantation (Futagawa & Terasaki 2006; Takahashi et al 2002; Tanabe et al 2003). Nevertheless, patient survival appears to be similar between ABOi and ABOc recipients in all of the included studies. One study highlighted that high preoperative maximum antibody titres are associated with graft loss (Tanabe et al 2003). The reason for this association remains unclear, but this association no longer exists when patients are treated with tacrolimus and mycophenolate mofetil (MMF) (Shimmura et al. 2005). Recipient age appears to affect graft survival as well, with younger recipients (≤ 29 years) achieving significantly better graft survival rates compared to older recipients (≥ 30 years) (Takahashi et al 2004).

ABOi recipients tended to have higher overall complication rates compared to ABOc recipients. The included studies highlighted that ABOi transplantation is associated with higher risks of antibody mediated rejection, which is expected considering the nature of this procedure. However, it is interesting to note that two studies reported similar rejection rates between ABOi and ABOc transplant recipients (Genberg et al 2007; Futagawa & Terasaki 2006).

Overall, the evidence indicates that ABOi kidney transplantation is feasible, with the potential of achieving similar graft and patient survival rates to ABOc transplantation. In addition, one study (Schwartz et al 2006) highlighted that ABOi transplantation should result in substantial cost savings compared to continual dialysis. Nevertheless, there are many issues that remain unresolved. The lack of standardisation across centres with regards to the transplantation protocol hinders comparisons across studies and makes it difficult to identify the “optimal” transplant procedure. Other issues that warrant further investigation is the necessity of splenectomy, the issue of over-immunosuppression, measurement of antibody titres and the phenomena of accommodation.

The availability of kidneys for transplant in Australia and New Zealand does not match the demand. Where people are willing to donate kidneys, over 30% of donor organs are incompatible with any available recipient. ABO incompatible (ABOi) transplantation is one strategy to increase the number of successful transplants in this context.

The development of immunosuppression programmes has shown an increasing success rate for graft retention where the donor and recipient are ABO incompatible, and ABOi graft retention rates are now comparable with those for ABO compatible (ABOc) transplants. Research shows that the safety of ABOi transplants is similar to that of ABOc transplants.

ABOi transplantation is now a valid and realistic option where no ABOc kidney is available. At the same time, alternative strategies to increase the number of kidneys available for transplant should also be considered. These include paired transplantation programmes using the combined population of Australia and New Zealand, and further promotion within the general community of the value of organ donation.

Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken a horizon scanning report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play regarding the introduction and use of ABO incompatible kidney transplantation (Register ID no. S000071).

ABO incompatible kidney transplantation can expand the donor pool to address the current shortage of transplant kidneys in Australia and New Zealand. The procedure is currently in limited use in Australia, and is still in the early stages of development.

This horizon scanning report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of ABO incompatible kidney transplantation, its present use, the potential future application of the technology, and its likely impact on the Australian healthcare system.

This horizon scanning report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with ABO incompatible kidney transplantation.

Chronic kidney disease

The kidney plays an essential role within the human body; it acts as a filter, controls the level of water and chemicals, produces hormones and clears waste products. Without functioning kidneys, the body would suffer from excessively high waste products and loss of chemical balance, resulting in disruption of important bodily functions. Chronic kidney disease (CKD) describes a condition in which the kidney suffers long-term damage that results in irreversible loss of kidney function. Individuals suffering from CKD are at risk of developing various complications and comorbidities, such as cardiovascular disease, respiratory system infection, anaemia and musculoskeletal problems (AIHW 2005).

The danger of CKD is that it remains almost asymptomatic until the very late stages of the disease. It develops over several years, and although there are commonly no symptoms it can lead to impairment of specific organs and therefore body systems, even in the early stages. As a complex chronic disease, CKD may arise from a variety of causes, such as glomerulonephritis, high blood pressure, polycystic kidney disease and diabetes. The pathway to the pathogenesis of CKD from these causes remains unclear; however, smoking, lack of exercise, poor nutrition and obesity all appear to contribute to the onset of CKD (AIHW 2005).

CKD patients whose kidney function is no longer capable of sustaining life are clinically defined as suffering from end-stage renal disease (ESRD). These patients usually undergo dialysis as an artificial means of removing waste from the body. While kidney transplantation is the only definitive treatment for ESRD, there are numerous hurdles to overcome before its implementation. Most notable of these is a shortage of donor organs, which has led to an increasing discrepancy between the number of ESRD patients on waiting lists and the number of available deceased donor kidneys (Beimler & Zeier 2007). Patients who remain on the transplant list (undergoing dialysis) have a significantly higher mortality rate largely due to the increased cardiovascular mortality rate in these patients (McDonald & Russ 2002). The need for suitable transplant organs is therefore critical, and warrants serious consideration. In an attempt to address this issue, the medical community has endeavoured to educate the public about donation with the hope of increasing awareness and subsequently the number of donors. Despite these efforts, there has been little improvement in the number of donors. In some countries, the number of available donor kidneys for transplantation has remained static for at least a decade (Holechek et al 2003).

It appears obvious that expanding the pool of living donors is the next logical step. Despite the fact that living kidney transplantations are more commonplace now due to the advancement of technology, a substantial proportion of suitable living donors are rejected due to pre-existing human leukocyte antigen antibodies

or ABO-incompatibility (Beimler & Zeier 2007). In fact, by virtue of the distribution of blood group types alone, approximately 35% of living donors would be rejected based on blood group incompatibilities (Crew & Ratner 2005). This is far from ideal considering the dire need for suitable donor kidneys worldwide.

In an attempt to overcome the problem of ABO incompatibility, clinicians have explored various protocols designed to address and increase the viability of ABO incompatible (ABOi) kidney transplantation. The key concept in ABOi kidney transplantation is the removal of anti-A/B antibodies within the recipient and the suppression of antibody production as well as reaction towards foreign blood group antigens (isoagglutinins) present on ABOi donor kidneys. It is interesting to note that ABOi transplantation has had a long history, dating back to the 1950s; however, the results of ABOi transplantation have generally been poor and inconsistent. Consequently, interest in ABOi transplantation has dwindled substantially over decades. Recent advances in technology and pharmacology has reignited interest in this technique, and has increased the feasibility of this procedure (Holocek et al 2003).

ABO blood groups and transplant rejection

There are four blood groups according to the ABO classification: A, B, O and AB. This classification is based on the presence or absence of inherited antigenic substances (proteins, glycoproteins, carbohydrates etc.) that are expressed on red blood cells. An individual will not have antibodies for the antigen present on his own cells; for example, a blood group A individual will have antibodies for B and O, but not A. Organ rejection after ABOi kidney transplantations are triggered by anti-blood type antibodies binding to renal vascular endothelial cells. This activates complement, platelet aggregation and inflammation, leading to intravascular thrombosis and occlusion of blood flow (Ishida et al 2003).

Acute organ rejection is the most prevalent cause of graft failure in ABOi kidney transplantation (Toma et al 2001). Acute rejection can be mediated by alloreactive inflammatory cells or allospecific antibodies. Although cell-mediated rejection has been traditionally recognised, research has revealed that acute antibody-mediated rejection is an important cause of graft failure. Acute antibody-mediated rejection was only recently recognized as a distinctive clinicopathological entity. It was not listed in both the original (1993) and revised (1997) Banff schemes for renal transplant diseases, but was officially added to this scheme in 2003. In some literature, acute antibody-mediated rejection may have been described under a variety of names, such as accelerated acute, delayed acute or delayed humoral rejection (Truong et al 2007).

Description of the procedure

As stated previously, depletion of circulating blood type antibodies and immunosuppression are the key steps to achieving successful ABOi kidney

transplantation. The removal of antibodies prior to transplantation is typically achieved via apheresis while immunosuppressive drug regimens are utilised to suspend antibody production. Both apheresis and immunosuppressive regimens are described below:

Apheresis therapy

Apheresis is a technique whereby blood is separated into its different components in order to collect or remove a specific component. In the case of ABOi transplantation, the components to be removed are anti-A/B antibodies. Several variations of apheresis therapy include:

a) Plasmapheresis

Plasmapheresis is essentially a type of apheresis used to separate plasma from blood. During plasmapheresis, whole blood is removed from circulation and the red cells are returned, usually in a saline solution. Double filtration plasmapheresis (DFPP) was developed as a mean of removing anti-A/B type antibodies more effectively, and involves the use of two hollow fibre filters with different pore sizes. The first filter separates plasma from whole blood during extracorporeal circulation and the red blood cells are returned to the patient. The extracted plasma is then directed towards the second filter (smaller pore size) which separates larger molecular substances that were able to penetrate the first filter. The different pore sizes of the filters are chosen based on the substances that are targeted for removal. The filtrate of the second filter is mixed with cell-rich blood in an extracorporeal line for re-infusion (Ishida et al 2003). Usually, several sessions of DFPP are necessary before transplantation in order to decrease immunoglobulin G (IgG) and immunoglobulin M (IgM) titres of anti-A and anti-B antibodies to an acceptable level.

b) Plasma exchange

Plasma exchange involves the replacement of a patient's plasma with another colloid solution such as purified protein fraction, a mixture of plasma proteins from which immunoglobulins and complement have been depleted and albumin solution or some other plasma. The process is similar to that of plasmapheresis, with the additional step of replacing the removed plasma with a suitable substance. This technique is the least expensive method of removing antibodies; however, it has several disadvantages, most notably the loss of physiological plasma components such as coagulation factors, hormones and antiviral/antibacterial IgG and IgM (Tyden et al 2007).

This procedure may also result in the induction of a hypercoagulable state. During the process, both coagulating factors and circulating coagulants are removed; the resulting stress from the procedure may cause increased synthesis of acute phase reactants which include coagulation factors but not antithrombin III (Ishida et al 2003).

c) Selective antibody depletion

Plasmapheresis and plasma exchange can be utilised in combination with other separation techniques to achieve targeted reduction of specific anti-blood antibodies (Ishida et al 2003). One example is selective plasmapheresis where blood is passed between electrodes that deplete charged molecules from plasma (Merkel et al 1971) while another is anti-HLA plasmapheresis combined with affinity adsorption of IgG with staphylococcal protein A (Palmer et al 1989). These techniques are currently rarely utilised in modern ABOi transplantation.

d) Immunoabsorption utilising affinity column

Another technique to achieve depletion of anti-blood antibodies is the use of synthetic carbohydrate antigens immobilised on solid phase columns followed by ABO-incompatible transplantations. Bennett et al (1987) utilised this technique as a means of depleting anti-A and anti-B antibodies from the recipient. The effectiveness of this technique is limited by the same factors as plasmapheresis. One other important factor is blood flow, as it must be sufficient to enable depletion of antibodies from a large fraction of blood during the time that the procedure is carried out (Ishida et al 2003).

Two immunoabsorption columns that appear to be particularly prominent in current ABOi kidney transplantations are Immunosorba® which adsorbs immunoglobulins and Glycosorb® which adsorbs the more specific anti-A/B antibodies regardless of immunoglobulin class or subclass (Tyden et al 2007).

Immunosuppressive regimens

In order to reduce the risk of rejection after ABOi transplantation, patients are often subjected to an immunosuppressive regimen either prior or immediately after transplantation. In comparison to ABO compatible (ABOc) transplantation, immunosuppression procedures for ABOi kidney transplantation are quite rigorous. Some centres utilise a quadruple drug regimen consisting of cyclosporine, steroids, azathioprine and anti-lymphocyte globulin concomitant with splenectomy. In Japan, approximately 50% of the 41 centres with a program for kidney transplantation across the ABO barrier utilise a quadruple drug immunosuppression regimen (Toma et al 2001). As pharmacological knowledge advanced, newer drugs such as mycophenolate mofetil (MMF) and tacrolimus were introduced. In some centres MMF has replaced azathioprine as the drug of choice, while tacrolimus is gradually supplanting cyclosporine in many centres around the world.

The procedure

There are several different protocols currently implemented to conduct ABOi kidney transplantation worldwide. Beimler and Zeier (2007) highlighted that there is a lack of standardisation among the different protocols available, with different approaches being utilised in different countries over the last decade.

The first stage of ABOi transplantation involves initial immunosuppression (prior to transplantation) which usually incorporates both pharmacological immunosuppression and antibody depletion (apheresis etc.). This phase is sometimes referred to as the desensitisation protocol and is usually performed 2-4 weeks prior to transplantation (Holoček et al 2003; Beimler & Zeier 2007). In Europe, particularly Sweden and Germany, the common procedure for this phase involves the use of specific anti-A or anti-B immunoadsorption columns (Glycosorb®) in combination with rituximab, an anti-CD20 monoclonal antibody (Beimler & Zeier 2007). Following transplantation, three more immunoadsorption sessions are performed over a period of nine days as a pre-emptive means of preventing early postoperative rebound of antibodies. In Japan, a combination of extracorporeal antibody removal and pharmacological immunosuppression (triple therapy¹) is performed prior to transplantation. During transplantation, the spleen is often removed as a means of preventing antibody rebound post-transplantation. In 2004, a desensitisation protocol without splenectomy was introduced in some centres. In contrast to the European method, Japanese centres do not perform antibody removal post-transplantation (Beimler & Zeier 2007). In America, the desensitisation protocol consists of plasmapheresis, cytomegalovirus (CMV) hyperimmune globulin and anti-CD20 administration without splenectomy. A single dose of rituximab is administered one or two days prior to transplantation, followed by immunosuppression with tacrolimus and mycophenolate mofetil. Post-transplantation, patients undergo three sessions of plasmapheresis/CMVig (Beimler & Zeier 2007).

Intended purpose

ABOi kidney transplantation was developed to address the continual shortage of donor kidneys; this shortage has resulted in an increasing discrepancy between the number of patients with ESRD on waiting lists requiring transplantation and the number of available deceased donor kidneys.

Clinical need and burden of disease

The incidence of CKD in Australia, although documented in several databases, remains unclear due to limitations in data collection. The 2001 National Health Survey did not collect the biomedical data required to determine the prevalence of CKD in accordance with the US Kidney Disease Quality Outcome Initiative (K/DOQI) definition. The results of the survey indicated that less than 0.5% of responders are suffering from long-term kidney disease. However, this is likely to be a gross underestimation of CKD, as many Australians may not be aware of the problem or have not been diagnosed by a clinician due to the lack of symptoms in less severe cases (AIHW 2005). A study by the Australian Diabetes, Obesity and Lifestyle (AusDiab) study utilised biochemical measures to explore the

¹ Calcineurin inhibitors, steroids and antimetabolites, which differ across centres on the basis of which immunosuppressive agents are administered.

prevalence of CKD in a 1999-2000 national survey of noninstitutionalised Australians aged 25 years and over. The study revealed that 11.2% of participants had a glomerular filtration rate (GFR) of less than 60ml/min/1.73m². In addition to this, a further 5.1% of participants had protein or blood in their urine without significantly reduced kidney function (Chadban et al 2003). If these conditions continued to persist for 3 months or longer, 16.3% of respondents would have met the K/DOQI criteria for CKD.

Although the actual prevalence of CKD (and hence ESRD) remains unclear, it is possible to examine the prevalence and incidence of *treated* ESRD. The Australian and New Zealand Dialysis and Transplant (ANZDATA) reported that at the end of 2003, a total of 13,625 individuals with ESRD were being treated in Australia. In the last 20 years, the number of people being treated for ESRD has more than tripled from 2,181 patients in 1981 to 13,625 patients in 2003, with an average 5.6% increase in prevalence of treated ESRD each year. ANZDATA reported that 1,953 individuals underwent kidney replacement therapy in 2003. The incidence of treated ESRD was substantially higher for males (1,150 cases, 118 per million population) compared to females (803 cases, 77 per million population) across all age groups (ANZDATA 2008).

As of January 2008, 1388 Australians are waiting for kidney transplants (Australian Donate 2008). In most Australian states, the average wait time for a kidney from a suitable deceased donor is approximately 4 years (AIHW 2005). Australia has one of the lowest rates of deceased-donor kidney transplants (11 donors per million population) compared to other developed countries (e.g. United States: 22.1 donors per million, France: 18.3 donors per million), and average wait times will deteriorate further unless the donor pool is extended. In 2003, 40% of transplanted kidneys were from living donors. In fact, living-donor transplants have increased by approximately 29% from 2000 to 2005 (AIHW 2005). Nevertheless, the discrepancy between the number of people awaiting kidney transplants and the number of organ donors remains an ongoing concern, given that 35% of living donors are excluded based on blood group incompatibilities (Crew and Ratner 2005).

Stage of development

Due to severe shortages of available deceased-donor organs, a large proportion of living ABOi transplantation has taken place in Japan. To date, more than 1000 Japanese patients have undergone ABOi kidney transplantation, accounting for approximately 18% of all living-donor kidney transplants (Takahashi 2007). European countries, particularly Sweden and Germany, have developed protocols for ABOi transplantation and have performed approximately 60 ABOi kidney transplants to date (Beimler & Zeier 2007). Meanwhile, in the United States the John Hopkins group established a protocol for ABOi kidney transplantation which does not require splenectomy. In Australia, the first ABOi kidney transplantation was conducted in 2006 in the Royal Melbourne Hospital, and therefore the procedure is still in the early stages of development.

Existing comparators

There are no direct comparators to ABOi kidney transplantation; however, it is often compared to conventional ABOc transplantation as a means to determine if graft and patient survival are equal.

An alternative to ABOi kidney transplantation are paired kidney exchange programs. Paired kidney exchange programs essentially enable two incompatible donor-recipients to “exchange” kidneys, resulting in the possibility of two compatible living donor transplants. Through paired exchange programs, the pool of kidney donors can be expanded to include live donors who might otherwise not have been afforded the opportunity to donate to a loved one. In addition to this, the program allows more recipients to benefit from living donor kidneys, and introduces a more cost-effective option compared to patients remaining on dialysis or undergoing desensitisation protocols or deceased donor transplantation (Waterman et al. 2006).

Clinical Outcomes

A total of nine comparative studies (Level III intervention evidence) investigating ABOi kidney transplantation were selected for inclusion in this report. The studies identified for inclusion were generally of good quality; however, some lacked detail with regards to the transplantation protocol used while several did not provide adequate detail on safety outcomes. It is important to note that key differences in transplantation protocols, types of drugs utilised, patient composition/baseline characteristics and other factors essentially prevent any useful comparison of results across these studies. Nevertheless, the clinical outcomes presented overall should provide useful insight into the viability of ABOi kidney transplantation and its associated risks or complications.

Of the included studies, five studies originated from Japan. The typical ABOi transplantation protocol for these studies consisted of preoperative antibody removal (immunoabsorption/plasmapheresis) and concurrent splenectomy during transplantation, followed by pharmacological immunosuppression posttransplantation. Two studies were conducted in Europe, with a typical protocol consisting of antibody removal (immunoabsorption) and preoperative pharmacological immunosuppression, followed by postoperative immunoabsorption or apheresis. The remaining two studies were conducted in the United States; in these studies patients underwent a combination of protocols which are detailed within Table 1.

The safety and efficacy outcomes of the nine included comparative studies are presented in Table 1.

Table 1: Comparative studies investigating the safety and efficacy of ABOi kidney transplantation.

Study	Patients details	Procedure	Effectiveness outcomes	Safety outcomes
Futagawa and Terasaki (2006) Los Angeles, United States Level III-3 intervention evidence	<p>ABO compatible <u>Deceased</u> N=59438 Donor age: 35.9±17.5 years Recipient age: 47.4±14.5 years</p> <p><u>Living</u> N=37612 Donor age: 39.5±10.8 years Recipient age: 41.3±16.1 years</p> <p>ABO incompatible <u>Deceased</u> N=201 Donor age: 35.3±17.0 years Recipient age: 47.7±12.6 years</p> <p>AB→A/O: 8 AB→B: 11 A2B→B: 5 A2→B/O: 56 A1/A→B/O: 93</p> <p><u>Living</u> N=191 Donor age: 41.0±10.7 years Recipient age: 43.8±15.4 years</p> <p>AB→A/O: 6 AB→B: 7 B→A,A2/O:58 A2B→B: 7 A2→B/O: 65 A1/A→B/O: 48</p>	Not stated. United Network Organ Sharing (UNOS) data file included patients from 256 centres utilising different ABOi transplantation protocols.	<p><u>Graft survival:</u> At 5-years, Kaplan-Meier curves and long rank tests indicate no difference between ABOi (66.9%) and ABOc (66.7%) transplants for graft survival rates.</p> <p><u>Graft survival (non-A2 compatible transplants)</u> Graft survival among A2 incompatible donors significantly lower when compared with non-A2 incompatible donors for <i>decreased</i> transplants (p = 0.002).</p> <p>Functional graft survival rates at 1 and 5 years were similar between non-A2 compatible donors (91.3% and 77.4%), A2 incompatible donors (86.5% and 60.5%) and ABOc transplants (91.8% and 73.6%)</p> <p><u>Graft survival ABOi living donors</u> At 5-years, graft survival in 191 ABOi donors was 66.2% vs. 79.5% for ABOc donors (p=0.006).</p> <p>In patients with >1 year survival, difference between ABOc and ABOi groups for long-term graft survival was not statistically significant (p=0.151)</p>	<p>ABO compatible <u>Rejection (1 year)</u> Decreased: 25.6% Living: 22.3%</p> <p>ABO incompatible <u>Rejection (1 year)</u> Decreased: 25.9% Living: 21.5%</p>

Table 1 -continued-

Study	Patients details	Procedure	Effectiveness outcomes	Safety outcomes
<p>Genberg et al 2007</p> <p>Huddinge, Sweden</p> <p>Level III-2 intervention evidence</p>	<p>ABO compatible 30 patients <u>Recipient age at transplantation:</u> 45.1 (±11.9) years <u>Donor age at transplantation:</u> 49.1 (±8.4) years</p> <p>ABO incompatible 15 patients <u>Recipient age at transplantation:</u> 35.1 (±14.3) years <u>Donor age at transplantation:</u> 52.8 (±10.3) years</p>	<p><u>Preoperative:</u> A/B antibody removal achieved via repeated antigen-specific immunoabsorption (Glycosorb) on pretransplantation day -6, -5, -2 and -1.</p> <p>Rituximab 375 mg/m² body surface area given on day -30 and oral immunosuppression (tacrolimus, mycophenolate mofetil, prednisolone) instituted on day -10.</p> <p>Intravenous immunoglobulin (Gammagard) 0.5g/kg body weight administered on day -1.</p> <p><u>Postoperative:</u> Immunoabsorption was conducted on days 2, 5, and 8.</p> <p>All patients received sulfametoazol for 6 months.</p> <p>ABOi patients received valganciclovir for 3 months followed by valaciclovir for another 9 months.</p>	<p>ABO compatible Graft survival: 90% Patient survival: 97%</p> <p>ABO incompatible Graft survival: 87% Patient survival: 100%</p> <p><u>Serum creatinine:</u> No significant difference noted between groups at 1, 2 and 3 years post-transplantation</p> <p><u>Glomerular filtration rate:</u> No significant difference between groups at 1, 2 and 3 years post-transplantation.</p>	<p>ABO compatible <u>Acute rejection:</u> 4 patients (one antibody mediated, three cellular mediated) <u>Infection:</u> 7 CMV, 1 EBV, 6 sepsis, 11 urinary tract infection, 1 <i>Clostridium difficile</i> colitis, 3 surgical wound infection</p> <p>ABO incompatible <u>Acute rejection:</u> 1 patient <u>Infection:</u> 1 CMV, 1 sepsis, 2 urinary tract infections, 2 surgical wound infection</p> <p><u>A/B antibody measurements:</u> Median IgG and median IgM reduced significantly at all time points (3-6 months, 6-12 months, 12-24 months, >24 months).</p>
<p>Gloor et al (2003)</p> <p>Minnesota, United States</p> <p>Level III-2 intervention evidence</p>	<p>ABO compatible 81 patients</p> <p>ABO incompatible 18 patients <u>A2 non-A recipient</u> A2→B: 2 (11%) A2→O: 8 (44%)</p> <p><u>Non-A2 donor to incompatible recipient</u> A1→O: 5 (28%) B→O: 2 (11%) B→A: 1 (6%)</p>	<p>First 8 A2 ABOi recipients did not receive pretransplant preparation. Subsequent 2 patients receive plasmapheresis and one patient underwent splenectomy.</p> <p>Non-A2 ABOi recipients all received plasmapheresis consisting of one plasma volume exchange on days -4, -2, -1 and 0. In addition, all non-A2 recipients underwent splenectomy at the time of transplantation.</p> <p>All ABOi recipients received antibody induction with rabbit anti-human T cell polyclonal antibody 1.5mg/kg/day for 10 days.</p>	<p>ABO compatible Graft survival: 96% (1 year) Patient survival: 99%</p> <p>ABO incompatible Graft survival: 89% (1 year) Patient survival: 94%</p> <p>A2 ABO incompatible Graft survival: 90% (1 year) Patient survival: 80%</p> <p>Non-A2 ABO incompatible Graft survival: 100% (1 year) Patient survival: 100%</p>	<p>ABO compatible Not reported</p> <p>ABO incompatible Antibody mediated rejection: 28% of patients. Antibody-mediated rejection was more common in recipients of A2 kidneys compared to non-A2 kidneys (40% vs. 13%).</p> <p>44% of patients had complications post-transplantation.</p>

Table 1 -continued-

Study	Patients details	Procedure	Effectiveness outcomes	Safety outcomes
		Maintenance immunosuppression was achieved with tacrolimus, mycophenolate mofetil and prednisolone.	<u>Graft function:</u> Similar between ABOi and ABOc groups.	
Schwartz et al (2006) Minnesota, United States Level III-3 intervention evidence	<p>ABO compatible 77 patients Age: 50.2 ± 13.72 years</p> <p>ABO incompatible 40 patients Age: 48.3 ± 14.8 years</p> <p>A1→B: 1 (2.5%) A1→O: 8 (20%) A2→B: 2 (5%) A2→O: 13(32.5%) A1B→A: 2(5%) A1B→O: 2(5%) B→A: 4 (10%) B→O: 8(20%)</p>	<p>For non-A2 transplants, plasmapheresis consisting of one plasma volume exchange was conducted on days -4, -2, -1 and 0. Number of exchanges estimated from baseline antibody levels to achieve a titre of 1:8 on the day of transplantation. Plasmapheresis performed post-transplantation as well for 2 weeks to maintain antibody titre of 1:16.</p> <p>First 8 ABOi A2 recipients did not undergo pretransplant conditioning (plasmapheresis etc). first 10 ABOi non-A2 recipients underwent splenectomy, after May 2003 no patients underwent splenectomy but received rituximab (375mg/m²) 1 week prior to transplantation.</p> <p>All recipients received antibody induction with rabbit antihuman T-cell polyclonal antibody, 1.5mg/kg/day for 10 days.</p> <p>Maintenance immunosuppression involved the use of tacrolimus, mycophenolate mofetil and prednisolone. No anticoagulants were administered as part of the ABOi protocol.</p>	<p>ABO compatible Graft survival: 96% (death censored) Patient survival: 97% (1 year)</p> <p>ABO incompatible Graft survival: 90% (death censored) Patient survival: 95% (1 year)</p>	<p>In both ABOi and ABOc groups, most patients experienced more than one complication. Total complication per patient (average number of complications per patient) was 2.7± 2.9 and 3.6 ± 3.4, for ABOc and ABOi respectively (not significant).</p> <p>Overall incidence of surgical complications was higher in ABOi group (p = 0.0399).</p> <p>Antibody mediated rejection was significantly higher in ABOi patients within the first 90 days post-transplantation compared to ABOc patients (30% vs. 3%).</p> <p>No humoral rejection episodes were observed within first month.</p> <p>Cellular rejection was noted in 6.5% of ABOi recipients, none in ABOc recipients.</p>

Table 1 -continued-

Study	Patients details	Procedure	Effectiveness outcomes	Safety outcomes
<p>Takahashi et al (2002)</p> <p>Japan</p> <p>Level III-2 intervention evidence</p>	<p>ABO compatible 756 patients</p> <p>ABO incompatible 100 patients</p>	<p>Not stated.</p> <p>Tacrolimus utilised as immunosuppressant.</p>	<p>ABO compatible Graft survival: 96.1%, 93.7%, 91.2% at 1, 2 and 3-years. Patient survival: 98.5%, 98.2%, 97.7% at 1, 2 and 3-years.</p> <p>ABO incompatible Graft survival: 83.2%, 83.2%, 83.2% at 1, 2 and 3-years. Patient survival: 96.7%, 96.7%, 96.7% at 1, 2 and 3-years.</p> <p>Tacrolimus dosing and trough levels No significant difference in tacrolimus trough levels between ABOc and ABOi patients.</p>	<p>Not reported</p>
<p>Takahashi et al (2004)</p> <p>Japan</p> <p>Level III-3 intervention evidence</p>	<p>ABO compatible 1055 patients 30 (1-71) years Donor's age: 52 (21-75) years</p> <p>ABO incompatible 441 patients Recipients age: 34 (6-71) years Donor's age: 54 (23-79) years</p> <p>AB→O: 4(1%) AB→A: 60(14%) AB→B: 47(11%) A→O: 139 (31%) A→B: 41(9%) B→O: 110(25%) B→A: 40(9%)</p>	<p>Antibody removal was achieved via plasmapheresis or immunoadsorption (Biosynsorb®). Most centres utilised DFPP. Antibody removal was performed 2-3 times prior to transplantation. Antibody removal is not done post-transplantation with the exception of a sudden rise of anti-A/B antibody titres within 1 week post-transplantation and in patients with a pathological diagnosis of antibody mediated rejection.</p> <p>Pharmacological immunosuppression consisted of a triple drug regimen: calcineurin inhibitor (ciclosporin or tacrolimus), steroid (methylprednisolone or prednisolons) and an antimetabolite (azarhioprine or mizoribine).</p> <p>Splenectomy was performed in 98% of patients.</p>	<p>ABO compatible <u>Graft survival</u>: 96%, 90%, 81%, 71% and 57% at 1, 3, 5, 7, and 9-years, respectively. <u>Patient survival</u>: 98%, 97%, 94%, 92% and 88% at 1, 3, 5, 7, and 9-years, respectively.</p> <p>ABO incompatible <u>Graft survival</u>: 84%, 80%, 71%, 65% and 59% at 1, 3, 5, 7, and 9-years, respectively. <u>Patient survival</u>: 93%, 89%, 87%, 85% and 84% at 1, 3, 5, 7, and 9-years, respectively.</p> <p><u>Graft survival according to recipient age</u>: Subgroup analysis indicates that recipients ≤29 years had</p>	<p>ABO compatible Not reported</p> <p>ABO incompatible <u>Rejection</u>: Episodes of rejection were noted in 256 patients (58%). Chronic allograft nephropathy was noted in 47 patients (16%).</p> <p><u>Complications</u>: Infection: 83 Gastrointestinal symptoms: 21 Diabetes: 15 Hepatitis/hepatic impairment: 9 Surgical complications: 8 Hypertension: 7 Lymphocele: 7</p> <p><u>Death</u>: 60 patients (13.6%) Main causes include:</p>

Table 1 –continued-

Study	Patients details	Procedure	Effectiveness outcomes	Safety outcomes
		<p>Anticoagulation therapy was administered in 223 patients (51%) post-transplantation. Consisting of a target dose of 250-300mg/day of nafamostat mesilate. Oral platelet aggregation inhibitor continuously given as long as graft remained viable.</p>	<p>significantly higher graft survival rates compared to those ≥ 30 years ($p < 0.001$).</p> <p><u>Graft survival according to the presence or absence of anticoagulation therapy:</u> Graft survival rates were significantly higher in patients who received anticoagulation therapy post-transplantation ($p < 0.01$).</p>	<p>Pneumonia: 14 Hepatic failure: 8 Heart failure: 7 Cerebral haemorrhage: 6 Multiple organ failure: 3</p>
<p>Tanabe et al (1998) Tokyo, Japan Level III-2 intervention evidence</p>	<p>ABO compatible 366 patients Recipient age: 32.4 (2-61 years)</p> <p>ABO incompatible 67 patients Recipient age: 34.9 (8-58) years</p> <p>A1→O: 23(34%) B→O: 19 (28%) A1B→A1: 7 (10%) B→A1: 8(12%) A1→B: 4 (6%) A1B→B: 4 (6%) A1B→O: 2 (3%)</p>	<p>Anti A/B antibodies were removed via 2 sessions of DFPP (-7 days) and 3-4 sessions of immunoadsorption before transplantation until IgG/IgM titers decrease to the level of 1:16 or below.</p> <p>The immunosuppressive regimen consisted of methylprednisolone, cyclosporine, azathioprine, antilymphocyte globulin and deoxypergualin.</p> <p>Splenectomy was performed at the time of transplantation for all cases.</p>	<p>ABOi patient survival was 93% at 1 year and 91% at 8 years. Similar to ABOc patients.</p> <p>Graft survival was 79% at 1, 2, 3, and 4 years, 75% at 5 and 6 years, and 73% at 7 and 8 years. ABOi transplant recipients had a significantly high rate of early graft loss up to 3 years but had equivalent graft loss by year 4.</p>	<p>ABO compatible <u>Graft loss:</u> 40 patients <i>Cause of graft loss</i> Acute rejection: 8 Chronic rejection 20 Glomerulonephritis: 1</p> <p>ABO incompatible <u>Graft loss:</u> 16 patients <i>Cause of graft loss</i> Acute rejection: 5 Chronic rejection: 5 Death with function: 3 Withdrawal of immunosupp: 3 <u>Deaths:</u> 5 patients Death with function occurred in 3 patients (duodenal cancer, malignant lymphoma and cerebral haemorrhage). Another patient died of ischemic colitis and another of cerebral haemorrhage after graft loss.</p> <p><u>Infection</u> CMV: 10 patients Urinary tract infection: 2 patients Herpes zoster: 2 patients Haemorrhagic cystitis: 3 patients</p>

Table 1 –continued-

Study	Patients details	Procedure	Effectiveness outcomes	Safety outcomes
Tanabe et al (2003) Tokyo, Japan Level III-2 intervention evidence	<p>ABO compatible 777 patients Recipient age: 32.5±13.1 years Donor age: 52.7 ± 11.0 years</p> <p>ABO incompatible 141 patients Recipient age: 34.9±12.3 years Donor age: 54.1 ± 11.2 years</p> <p>A1→B: 8(6%) A1→O: 47(34%) B→A1: 16(11%) B→O: 38(27%) A1B→A1: 18(18(13%) A1B→B: 11(8%) A1B→O: 2(1%)</p>	<p>Anti A/B antibodies were removed via DFPP and/or sessions of regular plasmapheresis before transplantation. Anti-A/B IgG and IgM titres were reduced to 1:32 or below. Immunoabsorption was performed utilising BiosynSorb®.</p> <p>Pharmacological immunosuppression was achieved with the administration of methylprednisolone, cyclosporine or tacrolimus, and azathioprine or mycophenolate mofetil. Prior to the use of mycophenolate mofetil, antilymphocyte globulin and deoxyspergualin were administered (1989-1999).</p> <p>In most cases before 1999, graft was exposed to 150 rad radiation on day 1, 3, and 5 post-transplantation. Splenectomy was performed on all patients with the exception of one (low anti-B IgG/IgM titres).</p>	<p>ABO compatible Graft survival: 96%, 85%, 67%, and 58% at 1, 5, 10, and 13 years. Patient survival: 99%, 97%, 92%, 91% at 1, 5, 10, and 13 years.</p> <p>ABO incompatible Graft survival: 82%, 76%, and 56% at 1, 5 and 10 years. Patient survival: 94%, 94%, 88%, 84% at 1, 5, 10, and 13 years.</p>	<p>ABO compatible Deaths: 41 (5.3%) Acute rejection: 377 (49%)</p> <p>ABO incompatible Deaths: 14 (9.9%) Acute rejection: 85 (60%) Chronic rejection: 12 (8.5%)</p>
Tyden et al (2007) Uppsala, Sweden & Freiburg, Germany. Level III-2 intervention evidence	<p>ABO compatible 274 patients</p> <p>ABO incompatible 60 patients</p> <p><u>Stockholm (n=26)</u> Recipient age: 30.8 (1-63) years</p> <p><u>Freiburg (n=21)</u> Recipient age: 45.3 (21-63) years</p> <p><u>Uppsala (n=13)</u> Recipient age:</p>	<p>Immunosuppression consisted of rituximab (375mg/m²) 4 weeks prior to immunoabsorption. Followed by triple-drug immunosuppressive protocol, tacrolimus, mycophenolate mofetil, and prednisolone: 7-10 days before immunoabsorption (GlycoSorb®).</p> <p>Anti-A/B antibodies were removed using antigen specific immunoabsorption (GlycoSorb). Four preoperative apheresis sessions were conducted aiming for a preoperative antibody titre of IgG<1:8.</p> <p>0.5g/kg of intravenous immunoglobulin was administered prior to transplantation.</p>	<p>ABO compatible Graft survival: 95% Patient survival: 98% Serum creatinine: 133 (53-360) umol/L Follow up: 21.1 (2-63) months</p> <p>ABO incompatible Graft survival: 97% Patient survival: 98% Serum creatinine: 127 (42-203) umol/L Follow up: 17.5 (2-61) months</p>	<p>ABO compatible Not reported</p> <p>ABO incompatible One patient died with functioning graft at 4 months due to Clostridium colitis.</p> <p>No late antibody rebound and no ABO antibody-mediated humoral rejections were observed.</p> <p>3 and 5 cases from Stockholm and Freiburg (respectively) were cancelled due to persistent high</p>

Table 1 -continued-

Study	Patients details	Procedure	Effectiveness outcomes	Safety outcomes
	46.3 (19-69) years Mismatches: 27 A1, 24 B and 9 A2 major mismatches	Postoperatively, three sessions of apheresis were conducted every three days (Uppsala patients only). Freiburg patients only underwent postoperative adsorption when signs of antibody rebound were evident (2 fold increase in antibody titre).		antibody titres after up to 9 GlycoSorb adsorptions.

Safety

In general, Schwartz et al (2006) noted that most kidney transplantation recipients experienced more than one complication, and there was a trend towards an increase in complication rates per patient in ABOi patients compared to ABOc patients (3.6 ± 3.4 vs. 2.7 ± 2.9 ; $P=0.18$). Surgical complications² were significantly more prevalent in ABOi patients (1.3 ± 1.6 vs. 0.7 ± 1.0 ; $P=0.0399$). However, Schwartz et al (2006) noted that of the specific medical complications assessed³, only the incidence of hypertension was significantly different, and it was more common in ABOc patients (24.7% vs. 7.5%; $P=0.026$). There was a trend of increased complications in patients who experienced antibody mediated rejection, as suggested by the observation that all 12 patients (100%) who had an episode of antibody-mediated rejection also had a medical or surgical complication. In comparison, complications occurred in 22/28 (79%) patients who did not experience antibody mediated rejection ($P=0.15$) (Schwartz et al 2006).

Gloor et al (2003) observed that 8/18 (44%) patients experienced complications during their posttransplantation course; however, no statistical comparisons were made between ABOi and ABOc recipients.

Rejection

Six studies reported on the incidence of rejection posttransplantation. The overall rejection rate ranged from 21% to 69% for ABOi recipients (Futagawa & Terasaki 2006; Genberg et al 2007; Gloor et al 2003; Schwartz et al 2006; Takahashi et al 2004; Tanabe et al 2003). Genberg et al (2007) noted no significant difference in acute rejection rates between ABOi and ABOc recipients. Similarly, Futagawa and Terasaki (2006) noted no difference in rejection rates between living or deceased ABOi and ABOc recipients 1 year post-transplantation; however, ABOi recipients suffered more graft losses compared to ABOc recipients within the first 30 days, which is attributed to humoral rejection as a result of inadequate antibody removal (Futagawa & Terasaki 2006).

Three other studies noted that antibody-mediated rejection was significantly more common in ABOi kidney recipients than ABOc recipients (Schwartz et al 2006; Tanabe et al 2003; Tanabe et al 1998). Tanabe et al (1998) reported that rejection was the most common cause of graft loss in both ABOc and ABOi recipients, accounting for 70% and 63% of graft loss respectively. This was further supported by a later study (Tanabe et al 2003).

There is some evidence that ABOi recipients with baseline anti-donor IgG antibody titres of $\leq 1:32$ are unlikely to experience antibody-mediated rejection regardless of donor blood group (Gloor et al 2003). The investigators noted that

² Wound, urologic, haemorrhagic, pulmonary, vascular, peripheral neuropathy and deep venous thrombosis.

³ Fluid/electrolyte, endocrine, infectious, hyperlipidaemia, hypertension, neurologic, dermatologic, psychiatric, cardiac, hematologic and medicine toxicity.

4/8 (50%) patients with an IgG titre of ≥ 128 experienced antibody-mediated rejection, which includes three patients who had received pretransplant plasmapheresis. All patients within this cohort who suffered antibody-mediated rejection despite pretransplant conditioning had anti-donor antibody titres $\geq 1:64$ at baseline and $\geq 1:8$ at the time of transplantation (Gloor et al 2003). In support of this, Tanabe et al (2003) noted that although ABOi recipients had serum anti-A/B IgG and IgM titres reduced to $\leq 1:32$ at the time of transplantation, 9/15 (69%) of patients with preoperative maximum anti-A/B IgG titres of more than 1:128 experienced graft loss. In fact, 33% of these patients with a high maximum IgG titre had graft loss due to acute rejection in the early posttransplant period. In contrast, of patients with a maximum titre of less than 1:64, 23/85 (27.1%) patients lost their graft and only 7/85 (8.2%) lost their graft to acute rejection (Tanabe et al 2003).

Infectious complications

Three studies reported infectious complications (Genberg et al 2007; Tanabe et al 1998; Takahashi et al 2004). Takahashi et al (2004) highlighted that 18.8% of ABOi recipients experienced infection; however, infection rates were not compared to ABOc transplant recipients and the severity was not presented. Grenberg et al (2007) stated there was no difference between ABOi and ABOc recipients with regards to the incidence of infectious complications and no patients developed *P. jiroveci* or any other invasive fungal infection (Genberg et al 2007). Tanabe et al (1998) reported an overall infection rate of 25% (17/67 patients); 10 patients (15%) had symptomatic CMV infection, but none suffered serious tissue invasive disease.

Effectiveness

The key measures of effectiveness for ABOi kidney transplantation are graft survival and patient survival. Patient survival was reported in seven of the included comparative studies, while graft survival was presented in all of the included studies.

Graft survival

Of the included studies, five studies reported similar graft survival rates between living ABOi and ABOc transplant recipients (Genberg et al 2007; Gloor et al 2003; Schwartz et al 2006; Takahashi et al 2002; Tyden et al 2007). In contrast, three studies (Futagawa & Terasaki 2006; Takahashi et al 2002; Tanabe et al 2003), reported significant lower graft survival in ABOi recipients compared to ABOc recipients.

Tanabe et al (2003) noted that graft survival rates were significantly lower in ABOi recipients up to 3 years posttransplantation (log-rank test, $P=0.007$). Meanwhile, Futagawa and Terasaki (2005) only observed a significantly lower graft survival rate in living ABOi recipients relative to living ABOc recipients ($P=0.006$) at 5 years (66.2% vs. 79.5%); no difference was noted between ABOi

and ABOc cadaver transplants. However, the significant difference in living-donor graft survival rates faded when long-term graft survival rates were restricted to patients who survived >1 year (Futagawa & Terasaki 2005).

An interesting observation noted by Tanabe et al (2003) is the potential influence of preoperative levels of anti-A/B IgG or IgM titres on graft survival. The authors reported that graft survival rates for patients with pretransplantation maximum anti-A/B IgG antibody titre of less than 1:16 were 75.5%, 66.2% and 59.6% at 1, 5 and 10 years respectively. Meanwhile, patients with titres ranging from 1:32-1:64 achieved graft survival rates of 87.4%, 84.7% and 60.2%. In contrast, patients with anti-A/B IgG titres >1:128 had substantially lower graft survival rates of 53.3%, 42.7% and 21.3% at 1, 5 and 10 years respectively. Analyses indicated that maximum anti-A/B IgG antibody titre prior to transplantation was a significant risk factor for long-term graft survival in ABOi recipients (log-rank test, $P=0.002$); however, this correlation has not been observed since 1998 for this cohort (Tanabe et al 2003). A similar pattern was observed by Gloor et al (2003), as the presented data suggests that *baseline* (prior to any treatment) IgG antibody titre is the greatest predictor of antibody-mediated rejection, which in turn provides an indication of graft survival. Within this patient group, the only graft losses occurred in two recipients of A2 kidneys with high baseline anti-A IgG antibody titres of 1:128 and 1:256 (Gloor et al 2003).

Recipient age appears to influence graft survival rates as well. Takahashi et al (2004) showed that high graft survival rates of 90%, 90%, 85%, 85% and 76% were achieved at 1, 3, 5, 7 and 9 years respectively in children aged ≤ 15 years at the time of transplantation. Meanwhile recipients aged between 16 to 29 years achieved graft survival rates of 90%, 85%, 76%, 74% and 74% at 1, 3, 5, 7 and 9 years respectively. Analyses indicated that graft survival rates were significantly higher in transplant recipients aged ≤ 29 years relative to recipients ≥ 30 years (log-rank; $p<0.001$) (Takahashi et al 2004). Conversely, an earlier publication by Takahashi et al (2002) did not observe any statistically significant difference in graft survival between patients aged <30 and >30 years, but highlighted a possible trend towards better graft survival in younger patients (no statistical details provided).

The administration of anticoagulant therapy appears to have some association to graft survival as well. All 223 patients who received concomitant anticoagulation therapy in the study by Takahashi et al (2004) had significantly higher graft survival rates (85%, 83%, 78%, 79% and 68% at 1, 3, 5, 7 and 9 years respectively) compared with those who were not given this therapy (82%, 75%, 62%, 56% and 42% at 1, 3, 5, 7 and 9 years respectively) ($p<0.01$).

Patient survival

All eight comparative studies which reported patient survival revealed that survival rates were comparable between ABOi and ABOc transplant recipients

(Genberg et al 2007; Gloor et al 2003; Schwartz et al 2006; Takahashi et al 2002; Takahashi et al 2004; Tanabe et al 1998; Tanabe et al 2003; Tyden et al 2007).

Long-term patient survival rates were reported in four studies (Takahashi et al 2002; Takahashi et al 2004; Tanabe et al 1998; Tanabe et al 2003). In all four studies, patient survival did not fall below 80%, while one study showed that ABOi recipient survival was comparable to ABOc recipients up to 13 years posttransplantation (Tanabe et al 2003).

Renal function

Only one of the included comparative studies (Genberg et al 2007) reported glomerular filtration rate (GFR) and serum creatinine as measures of renal function. Utilising the Cockcroft-Gault formula at 1, 2 and 3 years, GFR rates for ABOi recipients were 81.8, 82.4 and 79.7 mL/min respectively. In comparison, GFR rates for ABOc recipients were 77.4, 79.0 and 75.3 mL/min at 1, 2 and 3 years respectively. GFR was not significantly different between ABOi and ABOc recipients (Genberg et al 2007).

Serum creatinine levels at 1, 2 and 3 years were similar between ABOi (124.4, 122.8 and 132.3 $\mu\text{mol/L}$, respectively) and ABOc (121.2, 124.1 and 144.3 $\mu\text{mol/L}$ respectively) recipients as well (Genberg et al 2007). These outcomes indicate that renal function was comparable between ABOi and ABOc recipients.

Ongoing issues of ABOi transplantation

Although research on ABOi kidney transplantation has substantially contributed to the success of its implementation in several countries, there are several issues that remain ambiguous or unresolved. These issues will be discussed in greater detail in the following pages.

Over-immunosuppression

From the included comparative studies it is evident that different centres use a variety of methods to achieve adequate immunosuppression or desensitisation prior to transplantation. The variation in methodologies between centres makes it difficult to compare results between studies, and the lack of standardisation adds confusion as to which protocol is best.

One concern associated with pharmacological immunosuppression is over-immunosuppression. Over-immunosuppression has been shown to result in a high incidence of CMV or carinii pneumonia infections. Aikawa et al (1998) noted that the use of anti-lymphocyte globulin (ALG) or deoxyspergualin (DSG) with triple therapy based on cyclosporine or tacrolimus for posttransplant induction resulted in a high incidence of CMV or carinii infection. As a result of this, ALG and DSG have been excluded since 1995. When triple therapy based on tacrolimus, azathioprine and methylprednisolone was compared to quadruple therapy based on cyclosporine, azathioprine, methylprednisolone and ALG/DSG, the incidence of

acute rejections and CMV or carinii infection for triple therapy was comparable to quadruple therapy. Patient and graft survival were comparable as well. However, triple therapy patients did not experience hyperacute rejection or irreversible acute rejection, while 8.3% of quadruple therapy patients had delayed hyperacute rejection (Aikawa et al 1998). These results indicate that perhaps triple therapy is still over-suppressing the immune system, resulting in similar rates of acute rejections and CMV or carinii infection.

The necessity of splenectomy

The spleen plays a major role in the production of anti-A and anti-B antibodies. Therefore, the rationale for splenectomy is basically to reduce lymphoid tissue, therefore eliminating B cells in particular, which suppresses the production of anti-A/B antibodies. Historically, ABOi kidney transplantations are only performed after several preoperative sessions of plasmapheresis to remove existing anti-A/B antibodies followed by splenectomy and conventional triple drug immunosuppression. This practice was instituted due to the results of several classic studies that have shown that patients who do not undergo splenectomy have a high risk of graft loss as a result of irreversible vascular rejection (Alexandre et al 1985; Bannett et al 1987). Despite various efforts to reduce complications, it is inevitable that splenectomy will result in immunodeficiency, therefore exposing the recipient to various opportunistic infections that may be life threatening. With the advent of new and more effective pharmacological immunosuppressive agents, some researchers have begun debating the necessity of splenectomy.

The study by Gloor et al (2005) retrospectively examined ABOi kidney transplantations of patients who received pretransplant plasmapheresis and splenectomy at the time of transplant in comparison to patients who underwent a new protocol that involved pretransplant anti-CD20 antibody (rituximab) administration and a more intensive posttransplant plasmapheresis regimen (no splenectomy). All patients received a series of plasmapheresis treatments and intravenous immunoglobulin (100 mg/kg) prior to transplantation, with the aim of achieving a titre of $\leq 1:8$ at the time of transplantation. Patients not undergoing splenectomy received a full dose of rituximab prior to pretransplant plasmapheresis. Posttransplant, the non-splenectomised patients received plasmapheresis and intravenous immunoglobulin therapy on days 1 and 3 by protocol. This was repeated as required in order to maintain antibody titre of $\leq 1:8$ during the first and $\leq 1:16$ during the second postoperative week. Gloor et al (2005) reported that both splenectomised and non-splenectomised groups achieved similar graft and patient survival rates. In addition to this, there was no difference in antibody titre between patient groups at baseline, day of transplantation, 3 months and 12 months post-transplantation. Humoral rejection was evident in 2/11 (18%) non-splenectomised patients and 7/23 (30%) splenectomised patients; but the difference was not statistically significant (Gloor et al 2005). The results show that the proposed pretransplantation protocol combined with posttransplantation plasmapheresis achieves comparable outcomes

to splenectomy. This implies that splenectomy is not necessary with sufficient immunosuppression and maintenance of low antibody titres postoperatively.

Tyden et al (2005) designed a protocol without splenectomy, utilising antigen-specific immunoadsorption (GlycoSorb®), rituximab and a conventional triple drug immunosuppressive protocol (tacrolimus, MMF and prednisolone). A conditioning period of 10 days pretransplantation was instituted, beginning with a dose of rituximab followed by a full dose of tacrolimus, MMF and prednisolone. Antigen-specific immunoadsorption was conducted on pretransplantation days -6, -5, -2 and -1. Following the last session, 0.5 g/kg of intravenous immunoglobulin was administered. Three more apheresis sessions were conducted post-transplantation; extra sessions were considered if antibody titres increased significantly. All patients successfully received their transplants. Two patients (18%) developed antibody rebound after the first of four apheresis sessions, resulting in postponed transplantation (1 week) with an additional four and five sessions of apheresis respectively. Four patients (36%) required extra posttransplantation adsorption due to a two-fold rise in antibody titre; the remaining 7 patients (64%) received three preemptive adsorptions as per protocol. None of the patients experienced rejection, either humoral or cellular, and no late reappearance of antibodies were observed throughout follow-up (Tyden et al 2005).

A later study by Tyden et al (2006) introduced a variant of the protocol presented above. This protocol recommends a 1 month pretransplant conditioning period, starting with rituximab (375 mg/m²) at pre-transplant day -30, followed with a full dose of tacrolimus (0.2 mg/kg), MMF (2 g), and prednisolone (30 mg) from pre-transplant day -13. Antigen-specific immunoadsorption (GlycoSorb®) was performed on pre-transplant days -6, -5, -2 and -1. If antibody titres following the last pretransplantation session exceeded 1:8, additional immunoadsorption sessions are conducted. After the final immunoadsorption session, 0.5g/kg of intravenous IgG was administered. Posttransplantation, three preemptive apheresis sessions were conducted every three days. Standard triple-drug immunosuppressive protocol (tacrolimus, MFF and prednisolone) was administered post-transplantation. Every patient (n=21) treated with this protocol received their transplants successfully. Three patients experienced antibody rebound after the first session of pretransplant apheresis, which postponed the transplant for 1 week. In most patients (15/21, 71%), posttransplant preemptive apheresis went according to protocol. The remaining 6/21 patients (29%) had a postoperative rise in antibody titres, which requiring additional adsorption. There were no incidences of early rejection and no late reappearance of antibodies throughout the follow-up period.

Current research therefore indicates that splenectomy is not necessarily mandatory for successful ABOi kidney transplantation. With the introduction of new protocols involving the administration of powerful new pharmacological immunosuppressants and various methods of specific antibody removal, there is a

possibility that splenectomy will be excluded from future ABOi transplantation protocols. However, it is important to note that long-term results are currently unavailable.

Preoperative antibody titres

The influence of maximum preoperative anti-A/B antibody titres (prior to plasmapheresis) on graft survival after ABOi kidney transplantation was highlighted earlier in this report by the results presented by Tanabe et al (2003). However, Tanabe et al (2003) noted that the correlation between antibody titre and graft survival was no longer evident from 1998. The authors did not elaborate why the correlation was lost post-1998. However, it is interesting to note that MMF was utilised from 1999 onwards.

In a later study, Shimmura et al (2005) investigated if the utilisation of an immunosuppressive regimen involving the administration of tacrolimus, MMF and steroid, seven days prior to transplantation would negate the influence of preoperative anti-A/B antibody titres on graft survival. Patients receiving this new immunosuppression protocol (group 2) were compared to those who underwent an immunosuppression protocol using cyclosporine and azathioprine (group 1). The results revealed that both patient groups achieved similar graft and patient survival rates. Further analysis of graft survival did not reveal any correlation between preoperative maximum titre of anti-A/B IgM *or* IgG before plasmapheresis and graft survival in either patient group. However, preoperative anti-A/B IgG titres were significantly correlated with long-term graft survival in group 1. This relationship was not evident in group 2. The corresponding graft survival rates to preoperative antibody titres for groups 1 and 2 are presented below (Table 2 & 3):

Table 2: Preoperative IgG antibody titre levels and corresponding graft survival rates (Group 1).

IgG antibody titre	Graft survival	
	5 years	10 years
<1:32 (n=42)	85.7%	65.0%
1:64 (n=22)	81.8%	54.6%
>1:128 (n=14)	57.1%	37.5%

Log-rank test, p=0.0084

Table 3: Preoperative IgG antibody titre levels and corresponding graft survival rates (Group 2).

IgG antibody titre	Graft survival	
	1 year	5 years
<1:32 (n=26)	80.8%	63.9%
1:64 (n=20)	95.0%	95.0%
>1:128 (n=43)	93.0%	84.7%

Log-rank test, p=0.0750

In addition to this, the incidence of acute humoral rejection appeared to have a significant correlation to preoperative IgG titres in group 1 patients, but not for group 2 (Table 4):

Table 4: Preoperative IgG antibody titre levels and corresponding incidence of acute humoral rejection.

	N	<1:32	1:64	>1:128	p-value
Group 1	78	21.4%	22.7%	57.1%	0.0292
Group 2	89	34.6%	30.0%	22.6%	0.9467

A higher incidence of acute humoral rejection was observed in group 1 recipients with an anti-A/B IgG antibody titre of more than 1:128 than in those with a titre less than 1:64. No correlation was evident between the incidence of acute humoral rejection and antibody titre in group 2.

This study therefore indicates that the use of tacrolimus and MMF in an immunosuppressive protocol may result in much better long-term graft survival and eliminate the influence of preoperative antibody titre levels on graft outcomes. It is important to note, however, that the mechanism whereby high preoperative antibody titres actually influence graft survival remains unknown.

Measurement of anti-A/B antibodies

The accuracy of anti-A/B antibody measurements prior to transplantation is a crucial step to the process. The accuracy of this measurement is essential to determine the amount of apheresis or immunoadsorption done prior to transplantation, as well as to determine if the patient's antibody levels are sufficiently low during the day of transplantation. Tanabe (2007) reported that serial-doubling dilution of serum using a test tube technique appears to be the standard technique for determining anti-A/B antibody titres in most institutions. The Japanese ABO-incompatible Transplantation Committee noted that in a national survey of 30 Japanese transplant institutions, the difference between the maximum and minimum values were 32-fold for IgM and 256-fold for IgG. Despite instituting a standardised protocol, the committee reported that there is still an 8-fold difference in most institutions (Koyabashi and Saito 2006).

In an attempt to address this issue, Tanabe (2007) compared four antibody measurement techniques: the test tube technique, BioVue Column Agglutination technique, DiaMed-ID micro typing system and flow cytometry. The comparison revealed that flow cytometry had the best reproducibility of results with no measurement deviations. The authors postulated that different reagents utilised in the different assays may affect the sensitivity of the technique, however the flow cytometry technique did not involve any polymers that may promote reaction of the immune complex within the assay (Tanabe 2007).

Another issue relating to antibody levels is the lack of consensus with regards to a 'suitable' level of anti-A/B IgG or IgM titres on the day of transplantation, which was evident from the included studies. Tyden et al. (2007) aimed to achieve IgG titre of <1:8 on the day of transplantation while Tanabe et al. (2003) was willing to accept an upper limit of 1:32 for IgG and IgM titres. Both studies reported good

graft survival rates despite their differences in antibody titre levels during the day of transplantation. It is also very likely that variations in antibody measurement techniques may have contributed to these variations in 'acceptable' antibody titres.

Another issue relating to antibody levels is the lack of consensus with regards to a 'suitable' level of anti-A/B IgG or IgM titres on the day of transplantation, which was evident from the included studies. Tyden et al (2007) aimed to achieve IgG titre of <1:8 on the day of transplantation while Tanabe et al (2003) was willing to accept an upper limit of 1:32 for IgG and IgM titres. Both studies reported good graft survival rates despite their differences in antibody titre levels during the day of transplantation.

Accommodation

When ABOi kidney transplantations are successful, clinicians tend to attribute graft survival to accommodation. Accommodation describes the phenomena in which despite an increase in antibody titres after transplantation, the graft survives and does not experience rejection or decreased renal function. However, there is no scientific evidence that clearly elucidates this phenomenon of accommodation. Research has not provided a clear description of accommodation and the term glosses over the absence of clear understanding of the mechanisms involved in graft survival.

Takahashi (2005) postulated that ABO histo-blood group antigen-antibody interactions alone are not sufficient to explain the mechanism for delayed hyperacute onset or the establishment of accommodation. Instead, the function of ABO histo-blood group glycosyltransferase may explain the mechanism of delayed hyperacute rejection onset and the establishment of accommodation.

It is clear that research on the mechanism of accommodation will provide useful insights which may further improve ABOi kidney transplantation; however, at the time of writing, the mechanism of accommodation remains unclear.

Cost Analysis

Schwartz et al (2006) noted that the immunosuppression/desensitisation protocol and the treatment of humoral rejection were the major drivers of resource utilisation during the period of this study (1999 to 2003). The authors noted that an episode of humoral rejection significantly increases resource utilisation and hence cost in ABOi transplantation. The authors identified several items that were used in an increased manner during ABOi transplantation, this included plasmapheresis treatments, fresh frozen plasma, albumin, thymoglobulin doses and kidney biopsies, all of which were associated with the protocol of the centre. The number of surgeries for ABOi and ABOc recipients (1.6 ± 1.1 vs. 1.4 ± 0.8) and total hospitalisation (1.7 ± 1.06 vs. 1.7 ± 1.4) was similar. Schwartz and colleagues (2006) stated that there was a trend towards increased total hospital days in the first 3 months for ABOi recipients (15.3 ± 17.8 days vs. 10.4 ± 11.1 days; $P=0.121$) but the longer time for the patient in hospital appeared to reduce the need for outpatient visits for ABOi recipients (12.3 ± 5.6 visits vs. 14.5 ± 7.0 visits; $P=0.061$) (Schwartz et al 2006).

Utilising the Olmsted County Healthcare Expenditure and Utilisation Database, the mean cost for an ABOi recipient for the period from 14 days before transplant to 90 days post-transplant was determined to be US\$90,300 \pm 68,100 (range: US\$42,700 to US\$390,500) compared to US\$52,500 \pm 25,300 (range: US\$34,000 to US\$153,200) for an ABOc transplant. The average cost of an ABOi transplant was determined to be significantly greater compared to an ABOc transplant (difference: US\$37,800; 95% confidence interval [15.4-60.3]). Over 80% of the increased cost associated with ABOi transplantation was accounted for by eight main factors: nursing (increased US\$8800), pharmacy (US\$8600), apheresis (increased US\$3900), radiology (increased US\$3900), blood bank (increased US\$3300), laboratory medicine (increased US\$2300) and operating room (increased US\$2200) (Schwartz et al 2006).

When comparing the cost-effectiveness of ABOi to ABOc, it is important to consider the cost of dialysis and comparative graft survival. In this specific study, Schwartz et al (2006) highlighted that the mean waiting time for ABOc transplantation in this patient cohort would be approximately 5 years in the United States. Five years of dialysis would cost approximately US\$270,000. In comparison, ABOi transplantation would incur a cost of approximately US\$140,000 over 5 years (US\$90,000 for immunosuppression and US\$10,000 per year for other transplant-related medicines). Therefore, if the graft survives for 5 years, ABOi transplantation actually saves approximately US\$130,000 in ESRD treatment per patient. If it is assumed that the ABOi recipient will experience graft failure and return to dialysis at 3 years posttransplantation, Schwartz et al (2006)

estimated that the cost saving is still approximately US\$42,000 per patient over the 5-year period.

Informed Consent

ESRD patients who intend to undergo ABOi kidney transplantation must be informed of the risks associated with the procedure, particularly the risks associated with immunosuppression and the potential for rejection after transplantation. In addition to this, potential ABOi kidney recipients should be informed that there are several protocol variants worldwide, and that the procedure is constantly being revised or modified as knowledge and technological/pharmacological improvements emerge. Patients should be aware of the importance of compliance, as non-compliance to the pharmacological regimen will jeopardise graft survival and the patient's well-being.

Access Issues

ABOi kidney transplantation is a complex procedure, requiring a host of experts and essential medical equipment. This procedure can only be conducted at specialist hospitals with adequate expertise and is therefore limited to major metropolitan areas.

Training

Due to the fact that ABOi kidney transplantation is still in the early development stages in Australia and New Zealand, there is currently no nationally standardised protocol for ABOi kidney transplantation. The procedure requires a team of medical personnel, including transplant surgeons, pharmacist, nephrologist, and immunologists.

Clinical Guidelines

At the time of writing, no clinical guidelines for ABOi kidney transplantation were identified. CARI (Caring for Australians with Renal Impairment), a national evidence-based project that commenced in 1999 with funding from the pharmaceutical industry, is currently producing guidelines for living kidney donations. It is unclear when these guidelines will be completed and the current draft does not address ABOi kidney transplantation.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of health technology assessment; however, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A horizon scanning report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost-effectiveness of a technology.

In the context of a rapidly evolving technology, a horizon scanning report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of ABO incompatible kidney transplantation, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The sources utilised in this assessment are listed in Table 5. The medical literature was searched with the search terms outlined in Table 6 to identify relevant studies up to March 2008 in English only. In addition to this, major international health technology assessment databases and clinical trial registers were searched.

Table 5: Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University of Adelaide library
Australian Medical Index	University of Adelaide library
CINAHL	University of Adelaide

	library
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University of Adelaide library
Current Contents	University of Adelaide library
Embase	Personal subscription
Pre-Medline and Medline	University of Adelaide library
PyscINFO	Personal subscription
RACS electronic library	Personal subscription
Internet	
Blue Cross and Blue Shield Association's Technology Evaluation Center	http://www.bcbs.com/tec/
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca
Current Controlled Trials metaRegister	http://www.controlled-trials.com/
EuroScan	http://www.euroscan.bham.ac.uk/
Health Technology Assessment International	http://www.htai.org/
International Network for agencies for Health Technology Assessment	http://www.inahta.org
Medicines and Healthcare products Regulatory Agency (UK)	http://www.mhra.gov.uk/
US Food and Drug Administration, Center for Devices and Radiological Health	http://www.fda.gov/cdrh/index.html
US Food and Drug Administration, Manufacturer and User Facility Device Experience Database	http://www.fda.gov/cdrh/mUDE.html
UK National Research Register	http://www.nrr.nhs.uk/
Websites of specialty organisations	http://www.health.gov.au/ (Obesity guidelines) or http://www.obesityguidelines.gov.au

Table 6: Search terms utilised

Search terms
MeSH
Kidney transplantation, ABO blood-group system/immunology*, Blood group incompatibility

Text words

Kidney transplant*, Renal transplant*, ABO incompatible transplant*

Limits

English, human

Availability and Level of Evidence

The medical literature (Table 5) was searched utilising the search terms outlined in Table 6 to identify relevant studies and reviews until March 2008. In addition, major international health assessment databases were searched.

A total of nine comparative studies were retrieved for inclusion in this horizon scanning report. The profiles of the included studies are summarised in Appendix B.

Sources of Further Information

Searches on www.clinicaltrial.gov and Current Controlled Trials (www.controlled-trials.com) did not reveal any ongoing studies on ABOi kidney transplantation.

Conclusions

Although the actual prevalence of chronic kidney disease in Australia and New Zealand is unknown, it is a substantial health issue in the community. ESRD continues to be a substantial burden to the healthcare system, with ANZDATA indicating that 13,626 individuals were being treated for ESRD in 2003.

Considering that the average waiting time for a suitable deceased donor kidney is approximately four years in most Australian states, it is clear that the discrepancy in the number of patients awaiting transplantation and the availability of suitable donor kidneys will worsen if nothing is done to counter this situation. One way of increasing the donor kidney pool is to encourage living kidney donation. While there have been some encouraging results, with live donor transplants accounting for 41% of total transplantations in 2005, researchers have pointed out that approximately 35% of living donors are rejected based on blood group incompatibilities alone.

In the advent of the growing need for more donor kidneys, researchers have explored the possibility of living ABOi kidney transplantation as a means of expanding the donor pool. Earlier attempts at ABOi kidney transplantation were generally disappointing and often inconsistent. However, with the introduction of powerful immunosuppressive drugs and various methods of anti-A/B antibody removal, the medical community has once again attempted to overcome the ABOi barrier that has long prevented transplantation between donors and recipients of different blood groups.

Five of the included comparative studies reported that ABOi recipients had similar graft survival rates to ABOc recipients; however, three studies reported that ABOi recipients had significantly lower graft survival rates relative to ABOc recipients (Futagawa & Terasaki 2006; Takahashi et al 2002; Tanabe et al 2003). Overall, it appears that ABOi recipient are capable of achieving similar graft survival rates to ABOc recipients. Several interesting observations were highlighted in a few studies. Tanabe et al (2003) noted that high titres of preoperative anti-A/B antibodies were associated with graft loss. In addition to this, one study highlighted that recipient age appeared to be associated with graft survival as well (Takahashi et al 2004). Recipients who were aged ≤ 15 years had high graft survival rates, while statistical tests indicated that recipients aged ≤ 29 years had significantly higher graft survival compared to those aged ≥ 30 years (Takahashi et al 2004).

Patient survival was similar between ABOi and ABOc recipients in all of the included studies that reported this outcome. Meanwhile, one study noted that renal function appears to be comparable in ABOi and ABOc patients as well (Genberg et al 2007).

Safety outcomes were generally reported in a manner that lacked detail in most of the included studies. Nevertheless, one study reported that ABOi patients tended to have higher overall complication rates compared to ABOc patients (Schwartz et al 2006). In addition to this, surgical complications were significantly higher in ABOi patients and appear to be increased in patients who experienced antibody-mediated rejection. Three studies noted that antibody-mediated rejection was significantly more common in ABOi kidney transplantation, which was not surprising considering the innate risks associated with this procedure. Two studies (Grenberg et al 2007; Futagawa & Terasaki 2006) reported that rejection rates were similar between ABOi and ABOc recipients throughout the follow-up period. However, it is important to note that despite similar incidence of rejection at 1 year posttransplantation, ABOi recipients experienced higher graft loss within the first 30 days after transplantation, which was attributed to antibody-mediated rejection (Futagawa & Terasaki 2006). Infectious complications were similar between ABOi and ABOc patients (Grenberg et al 2007).

Overall, the evidence indicates that ABOi kidney transplantation is feasible and is capable of achieving similar graft survival rates compared to ABOc transplantation. However, it is important to note that ABOi kidney transplantation is still a relatively new procedure and is continually revised with the introduction of new immunosuppressive drugs or other technological advances. There is continual debate with regards to several aspects of the procedure, such as the necessity of splenectomy and the optimal protocol for ABOi transplantation. The lack of standardisation worldwide continues to prevent comparisons across studies and hinders the elucidation of the most effective transplantation protocol. Furthermore, the large variation in antibody titre measurements as reported by Kotobashi and Saito (2006) highlights the possibility that there are many technical issues that can influence important steps of the transplantation procedure. This inconsistent measurement of antibody titres is one example that may explain the different perceptions among various centres with regards to the 'suitable/acceptable' antibody titre on the day on transplantation. In addition to this, the long-term outcomes of new drugs such as MMF, rituximab and tacrolimus that are currently utilised in most modern ABOi transplantation procedures has not been established. It is therefore clear that further research is necessary to determine the most effective protocol for ABOi transplantation. Nevertheless, the evidence available to date on ABOi kidney transplantation is encouraging, and it appears to be a viable procedure to address the growing discrepancy between the pool of suitable donor kidneys and ESRD patients requiring transplantation to survive.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention §	Diagnosis **	Prognosis	Aetiology †††	Screening
I †	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among consecutive patients with a defined clinical presentation ††	A prospective cohort study †††	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among non-consecutive patients with a defined clinical presentation ††	All or none ††††	All or none ††††	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial † Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study † Interrupted time series without a parallel control group	Diagnostic case-control study ††	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ††	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

‡ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au.

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

†† Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; Lijmer et al 1999; Phillips et al 2001; Bannister et al 2001; Bannister et al 2002; Bannister et al 2003; Bannister et al 2004; Bannister et al 2005; Bannister et al 2006; Bannister et al 2007; Bannister et al 2008; Bannister et al 2009; Bannister et al 2010; Bannister et al 2011; Bannister et al 2012; Bannister et al 2013; Bannister et al 2014; Bannister et al 2015; Bannister et al 2016; Bannister et al 2017; Bannister et al 2018; Bannister et al 2019; Bannister et al 2020; Bannister et al 2021; Bannister et al 2022; Bannister et al 2023; Bannister et al 2024; Bannister et al 2025

Appendix B: Profiles of studies

Study	Location	Study design	Study population	Patient demographics	Outcomes assessed
Futagawa and Terasaki (2006)	Los Angeles, United States	Level III-3 intervention evidence	ABO_c Deceased: 59438 Living: 37612 ABO_i Deceased: 201 Living: 191	ABO_c Deceased: Donor age: 35.9±17.5 years Recipient age: 47.4±14.5 years <u>Living</u> Donor age: 39.5±10.8 years Recipient age: 41.3±16.1 years ABO_i <u>Deceased</u> Donor age: 35.3±17.0 years Recipient age: 47.7±12.6 years <u>Living</u> N=191 Donor age: 41.0±10.7 years Recipient age: 43.8±15.4 years	Graft survival, rejection
Genberg et al. 2007	Huddinge, Sweden	Level III-2 intervention evidence	ABO_c 30 patients ABO_i 15 patients	ABO_c <u>Recipient age at transplantation:</u> 45.1 (±11.9) years <u>Donor age at transplantation:</u> 49.1 (±8.4) years ABO_i <u>Recipient age at transplantation:</u> 35.1 (±14.3) years <u>Donor age at transplantation:</u> 52.8 (±10.3) years	Graft survival, patient survival, renal function (serum creatinine, GFR), acute rejection, infection and antibody levels
Gloor et al. (2003)	Minnesota, United States	Level III-2 intervention evidence	ABO_c 81 patients ABO_i 18 patients	Not stated	Graft survival, patient survival, rejection, graft function, overall complications
Schwartz et al. (2006)	Minnesota, United States	Level III-3 intervention evidence	ABO_c 77 patients ABO_i 40 patients	ABO_c Age: 50.2 ± 13.72 years ABO_i Age: 48.3 ± 14.8 years	Graft survival, patient survival, complication rates, surgical complications, rejection

Takahashi et al. (2002)	Japan	Level III-2 intervention evidence	ABOc 756 patients ABOi 100 patients	Not stated	Graft survival, patient survival, Tacrolimus dosing and trough levels.
Takahashi et al. (2004)	Japan	Level III-3 intervention evidence	ABOc 1055 patients ABOi 441 patients	ABOc Recipient age: 30 (1-71) years Donor age: 52(21-75) years ABOi Recipient age: 34 (6-71) years Donor age: 54 (27-79) years	Graft survival, patient survival, patient survival according to age, rejections, complications
Tanabe et al. (1998)	Tokyo, Japan	Level III-2 intervention evidence	ABOc 366 patients ABOi 67 patients	ABOc Recipient age: 32.4 (2-61) years ABOi Recipient age: 34.9 (8-58) years	Graft survival, patient survival, rejection, infection, causes of graft loss
Tanabe et al. (2003)	Tokyo, Japan	Level III-2 intervention evidence	ABOc 777 patients ABOi 141 patients	ABOc Recipient age: 32.5±13.1 years Donor age: 52.7 ± 11.0 years ABOi Recipient age: 34.9±12.3 years Donor age: 54.1 ± 11.2 years	Graft survival, patient survival, rejection
Tyden et al. (2007)	Uppsala, Sweden & Freiburg, Germany.	Level III-2 intervention evidence	ABOc 274 patients ABOi 60 patients	ABOc Not stated ABOi <u>Stockholm (n=26)</u> Recipient age: 30.8 (1-63) years <u>Freiburg (n=21)</u> Recipient age: 45.3 (21-63) years <u>Uppsala (n=13)</u> Recipient age: 46.3 (19-69) years	Graft survival, patient survival, serum creatinine, rejection

Appendix C: HTA internet sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
<http://www.med.monash.edu.au/healthservices/cce/evidence/>
- Health Economics Unit, Monash University
<http://chpe.buseco.monash.edu.au>

AUSTRIA

- Institute of Technology Assessment / HTA unit
<http://www.oeaw.ac.at/ita/welcome.htm>

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) <http://www.aetmis.gouv.qc.ca/en/>
- Alberta Heritage Foundation for Medical Research (AHFMR)
<http://www.ahfmr.ab.ca/publications.html>
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
<http://www.cadth.ca/index.php/en/>
- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database <http://www.mycabot.ca>
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University <http://www.chepa.org>

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia <http://www.chspr.ubc.ca>
- Health Utilities Index (HUI) <http://www.fhs.mcmaster.ca/hug/index.htm>
- Institute for Clinical and Evaluative Studies (ICES) <http://www.ices.on.ca>

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp
- Danish Institute for Health Services Research (DSI) <http://www.dsi.dk/engelsk.html>

FINLAND

- Finnish Office for Health Technology Assessment (FINOHTA) <http://finohta.stakes.fi/FI/index.htm>

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) <http://www.anaes.fr/>

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA <http://www.dimdi.de/dynamic/en/>

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
<http://www.gr.nl/adviezen.php>

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
<http://nzhta.chmeds.ac.nz/>

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
<http://www.kunnskapssenteret.no/>

SPAIN

- Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud “Carlos III” / Health Technology Assessment Agency (AETS)
http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp
- Catalan Agency for Health Technology Assessment (CAHTA)
<http://www.aatrm.net/html/en/dir394/index.html>

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
<http://www.sbu.se/www/index.asp>
- Center for Medical Health Technology Assessment
<http://www.cmt.liu.se/>

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
<http://www.snhta.ch/>

UNITED KINGDOM

- NHS Quality Improvement Scotland
<http://www.nhshealthquality.org>
- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)
<http://www.hta.nhsweb.nhs.uk/>
- University of York NHS Centre for Reviews and Dissemination (NHS CRD)
<http://www.your.ac.uk/inst/crd/>
- National Institute for Clinical Excellence (NICE)
<http://www.nice.org.uk/>

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
<http://www.ahrq.gov/clinic/techix.htm>
- Harvard School of Public Health – Cost-Utility Analysis Registry
<http://www.tufts-nemc.org/cearegistry/index.html>
- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)
<http://www.bcbs.com/tec/index.html>

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