Specialist Working Group for Solid Organ Transplantation

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Kidney transplantation**	**Kidney transplantation**	
Specialty	Transplantation Medicine	Transplantation Medicine	
Chapter	6	6	
Specific Conditions		i. 1st kidney ii. 2nd kidney iii. 3rd kidney iv. 4th kidney v. Liver & Kidney vi. Heart & Kidney vii. Pancreas & kidney viii. Other	Specific condition field will be used to track the complexity of kidney transplant for data analysis from the Ig System.
Level of Evidence	Clear evidence of benefit (Category 1).	Clear evidence of benefit (Category 1).	
Justification for Evidence Category	An RCT enrolling adult patients with end stage renal disease (ESRD) who were highly sensitised to HLA antigens found that IVIg was better than placebo in reducing anti-HLA antibody levels in highly sensitised patients	An RCT enrolling adult patients with end stage renal disease (ESRD) who were highly sensitised to HLA antigens found that IVIg was better than placebo in reducing anti-HLA antibody levels in highly sensitised patients	

	with ESRD (followed for two years after transplant), and that transplant rates were improved with IVIg therapy (Jordan et al 2004). Multiple case series have been reported in the literature, indicating efficacy in (acute) antibody mediated rejection, and recommended by a consensus conference (Takemoto et al 2004). Jordan et al (1998) combined data from seven renal transplant recipients and three heart transplant recipients with steroid-resistant combined antibody-mediated and cellular rejection. All patients in this series were successfully treated with high-dose IVIg. A small RCT of transplanted patients with a five-year follow-up period showed that IVIg was as effective as OKT3 monoclonal antibodies in the treatment of steroid resistant rejection (survival rate at two years was 80% in both groups) but IVIg generated fewer side effects (Casadei et al 2001).	with ESRD (followed for two years after transplant), and that transplant rates were improved with IVIg therapy (Jordan et al 2004). Multiple case series have been reported in the literature, indicating efficacy in (acute) antibody mediated rejection, and recommended by a consensus conference (Takemoto et al 2004). Jordan et al (1998) combined data from seven renal transplant recipients and three heart transplant recipients with steroid-resistant combined antibody-mediated and cellular rejection. All patients in this series were successfully treated with high-dose IVIg. A small RCT of transplanted patients with a five-year follow-up period showed that IVIg was as effective as OKT3 monoclonal antibodies in the treatment of steroid resistant rejection (survival rate at two years was 80% in both groups) but IVIg generated fewer side effects (Casadei et al 2001).	

Description and Diagnostic Criteria There should be no change the published text	Transplant rejection occurs when a recipient's immune system attacks a transplanted organ or tissue. Despite the use of immunosuppressants, one or more episodes of rejection can occur after transplantation. Both cellular and humoral (antibody-mediated) effector mechanisms can play a role. The presence and pattern of rejection need to be established by biopsy. Laboratory tests to assess the presence and strength of antibodies to the donor antigens can provide additional useful information. Clinical assessment, blood tests, ultrasound and nuclear imaging are used primarily to exclude other causes of organ dysfunction. Acute cellular rejection occurs in 15–30% of renal transplants and is responsive to steroids in more than 90% of cases. When rejection is steroid resistant, IVIg is a safer therapy than anti-T cell antibody therapy with equal efficacy. Antibody mediated rejection (AbMR) occurs	Transplant rejection occurs when a recipient's immune system attacks a transplanted organ or tissue. Despite the use of immunosuppressants, one or more episodes of rejection can occur after transplantation. Both cellular and humoral (antibody-mediated) effector mechanisms can play a role. The presence and pattern of rejection need to be established by biopsy. Laboratory tests to assess the presence and strength of antibodies to the donor antigens can provide additional useful information. Clinical assessment, blood tests, ultrasound and nuclear imaging are used primarily to exclude other causes of organ dysfunction. Acute cellular rejection occurs in 15–30% of renal transplants and is responsive to steroids in more than 90% of cases. When rejection is steroid resistant, IVIg is a safer therapy than anti-T cell antibody therapy with equal efficacy. Antibody mediated rejection (AbMR) occurs	Reference added to include BANFF criteria - the international standard for diagnostic features of antibody mediated rejection (AbMR). (A)

	in 5–10% of renal transplants that have been performed with a compatible cross match. Before the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in most cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in more than 85% of patients.	in 5–10% of renal transplants that have been performed with a compatible cross match. Before the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in most cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in more than 85% of patients. Diagnostic criteria for AbMR must be consistent with Banff Criteria (Banff 2013 Meeting Report American Journal of Transplantation 2014 :14;272-283 page 277).			
Diagnosis is required	No	No	By which speciality	N/A	
Diagnosis must be verified		No	By which speciality	N/A	
Exclusion Criteria					
Indications	**Pre-transplantation** Patients in whom an antibody or antibodies prevent transplantation (donor specific anti-human leukocyte antigen (HLA) antibody/ies	**Pre - transplant where donor specific antibody/ies prevent transplantation (HLA or anti-blood group)** **Post-transplant - acute anti-body mediated**			Indications have been changed with the second indication removing eligibility for steroid resistant acute cellular rejection. Ig is rarely used for this requirement and if patients were very

	or anti-blood group antibody). **Post-transplantation** To treat steroid-resistant acute rejection which may be cellular or antibody mediated. For prevention and/or treatment of rejection where other therapies are contraindicated or pose a threat to the graft or patient.	**rejection** **Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient**	ill, could be managed under the third indication.
Qualifying Criteria	**Pre-transplantation** Patients in whom an antibody or antibodies prevent transplantation (donor-specific anti-HLA antibody/ies or anti-blood group antibody). **Post-transplantation** 1. Biopsy proven cellular rejection unresponsive to steroids with clinical evidence of graft dysfunction; OR 2. Acute antibody mediated rejection with clinical evidence of graft	**Pre - transplant where donor specific antibody/ies prevent transplantation (HLA or anti-blood group)** ABO incompatible transplant planned and/or HLA antibody / antibodies (minimum of 500 MFI) prevent organ transplantation **Post-transplant - active acute anti-body mediated rejection** Presence of incompatible ABO blood group donor specific antibody/antibodies and/or donor specific HLA antibody / antibodies (at	Eligibility criteria are more clearly defined and will greatly improve availability of data for future analysis (A) The relevant strength of HLA donor specific antibody(ies) has been under significant discussion within the SWG. Given the lack of strong evidence to support a definitive level, the qualifying value has been set at 500MFI and will be reviewed after 6-12 months of data collection and analysis. The presence of ABO or HLA antibodies and biopsy evidence (where relevant) have been included. Data will become available

	dysfunction; OR 3. As treatment or prophylaxis for rejection where conventional immunosuppressive therapy is contraindicated, for example: • in a patient with life-threatening infection in whom conventional immunosuppression will place the patient at even greater risk; • when the transplant is at risk (e.g. due to BK virus infection).	least a minimum of 500 MFI) AND Current clinical and laboratory evidence of graft dysfunction where biopsy is not available OR Organ biopsy demonstrates antibody mediated rejection according to Banff criteria[1] OR There is a high clinical suspicion that it is antibody mediated rejection and evidence is not yet available (one-off request in early period of acute rejection). For 2nd dose, DSA must be proven and biopsy must be abnormal but may not yet meet all of the Banff [1] diagnostic criteria. For subsequent doses, Banff[1] criteria on biopsy must be met. 1. *Banff 2013 Meeting Report American Journal of Transplantation 2014 :14;272-283 page 277*.	regarding triggers for Ig use. Eligibility criteria have been revised to clearly differentiate between different patient groups that exist within indications (A) Donor specific antibodies may be known prior to transplant or may develop post transplant. Criteria must accommodate both physiological pathways for disease. Where a DSA is newly developing, HLA results may not be available immediately. In some instances, biopsy results may be unavailable or non-diagnostic in the early stages where treatment is required. Acceptable contra-indication reasons

		Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient Conventional immunosuppressive therapy is contraindicated and reason is provided.	include: i. Significant infection or sepsis ii. Potential for life threatening infection iii. Life threatening condition iv. Malignancy v. Marrow suppression and cytopenia Detail of the reason to be provided.
Review Criteria	• Allograft organ function tests. • Biopsy response. • Laboratory monitoring of anti-HLA antibody and/or anti-blood group antibody responses. • Duration of graft and patient survival. • Reversal of clinical graft dysfunction.	**No review is required for one-off dosing**	Given that treatment is mostly by multiple single doses, very limited outcome data is likely to be collected within the system. Significant data is already available on transplant outcomes in other national systems - the potential to interface the Ig System such databases will be considered in future.
Dose	**IVIg with plasma exchange:** 0.1 to 0.5 g/kg post exchange. **IVIg alone:** 2 g/kg to a maximum of 140 g as a single dose, or 2 to 3.5 g/kg in a divided dose. When IVIg is used alone, further doses may	**IVIg with plasma exchange** 0.1 to 0.5 g/kg after each exchange (Total maximum dose of 2.5g/Kg divided across 5 doses) **IVIg without plasma exchange (single dose)** Up to 2 g/kg to a maximum of 140 g as a single dose.	Dosing specifications have been more explicitly defined (within current policy allowances) to support current clinical practices and accommodate the variable approaches to treatment protocols in use nationally. (A) Data will be available for analysis in future that will support the identification of better

	be warranted two to four weeks after initial therapy depending on clinical response and/or biopsy findings. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	**IVIg without plasma exchange (divided dose)** 2 to 3.5g/kg in a divided dose The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.**	practice.

POTENTIAL OPERATIONAL IMPACT			
No operational impact is anticipated.			
POTENTIAL IMPACT ON DEMAND			
Patient Numbers **& Usage** **2013-14**	**Patients treated:** 342 post tx (2%) 91 pre-tx (<1%) **Usage : 1%**	No impact on demand is expected from these changes. There is unlikely to be significant change in variable practice until data becomes available for analysis to compare differences in usage and identify contributing reasons.	
POTENTIAL IMPACT ON COST			
Current cost		**Anticipated reduction in cost, if any**	**Marginal**

		Marginal = borderline or unchanged from current cost **Minor** = decrease by $500K - $1.99M from current cost **Major** = decrease $2M+ from current cost	

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