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	**Solid Organ transplantation (Other than Kidney)**	**Solid Organ transplantation (Other than Kidney)**	While usage is quite low (<1%), it is recognised to be increasing each year, in line with the increased number of organ transplants becoming available and the increased complexity of transplants now being undertaken (as for kidney transplantation). Given that this is an evolving clinical area, it is recommended that a controlled decision path be used for eligibility criteria so that data will be available for analysis and usage is controlled within the same parameters being used for kidney transplantation which is consistent with current clinical practice.
Specialty	Transplantation	Transplantation	
Chapter	7	6	Recommendation to change 'chapter' is due to the desire to use a more structured approach to qualifying criteria. (A)
Specific Conditions		• Heart • Lung • Heart & Lung • Liver • Heart kidney	The types of combinations of organ transplants will be captured for data analysis (A)

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		• Heart liver • Liver kidney • Pancreas • Small intestine	
Level of Evidence	Small case studies only; insufficient data (Category 4a)	Small case studies only; insufficient data (Category 4a)	Unchanged
Justification for Evidence Category		Jordan et al (1998) combined data from seven renal transplant recipients and three heart transplant recipients with steroid-resistant combined antibody-mediated (AbMR) and cellular rejection. All patients in this series were successfully treated with high-dose IVIg. Findings from an International Consensus Conference in 2011 noted that IVIg has never been systematically studied in patients after transplant to prophylactically reduce the incidence of AbMR. Despite being routinely used for the treatment of AbMR, only 1 study has reported the efficacy of Ig therapy in this setting. Five patients with evidence of AbMR were treated with a combination of IVIg and plasmapheresis. Hemodynamics initially improved in all 5	Evidence revised to include reference to consensus conference small series. This section is likely to strengthen in future editions given the increased transplantation being supported internationally and in Australia. (A)

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		patients, but 2 patients later required further therapy with rituximab because of recurrent hemodynamic rejection.	
Description and Diagnostic Criteria		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 organ 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	Diagnostic requirements have been developed and for AbMR, are to comply with IHSLT diagnostic criteria. (A)

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		antibody therapy with equal efficacy. Antibody mediated rejection (AbMR) occurs in 10–20% of heart transplants that have been performed with a compatible cross match. AbMR is associated with increased incidence of graft dysfunction, coronary allograft vasculopathy and mortality. 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 the International Society for Heart and Lung Transplantation (IHSLT) Criteria (2011).	
Diagnosis is required	None specified.	No / By which speciality	No change.
Diagnosis must be verified		No / By which speciality	
Exclusion Criteria			

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Indications	IVIg may be indicated in: • highly sensitised patients awaiting transplantation; • transplant recipients with acute antibody-mediated rejection with clinical evidence of graft dysfunction; and • transplant recipients 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 greater risk, or when the transplant is at risk.	**Pre - transplant where donor specific antibody/antibodies prevent transplantation (HLA or anti-blood group) in highly sensitised patients** **Post-transplant - acute anti-body mediated rejection with clinical evidence of graft dysfunction** **Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient**	Indications are consistent with kidney transplantation and existing criteria for this condition.
Qualifying		**Pre - transplant where donor specific**	

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Criteria		**antibody/antibodies prevent transplantation (HLA and/or anti-blood group)** ABO incompatible transplant planned with or without HLA antibody or antibodies (minimum of 500 MFI) preventing organ transplantation. **Post-transplant - active acute antibody mediated rejection** Presence of incompatible ABO blood group donor specific antibody/antibodies and/or donor specific HLA antibody / antibodies (at least a minimum of 500 MFI) AND Current clinical and laboratory evidence of graft dysfunction where biopsy not available OR	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 and will be reviewed after 6-12 months of data collection and analysis. (A)

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		Organ biopsy demonstrates antibody mediated rejection according to Banff or IHSLT criteria[1] OR There is a high clinical suspicion that it is antibody mediated rejection and evidence not yet available (one-off request in early period of acute rejection). For a 2nd dose, Donor Specific Antibody(ies) must be proven and biopsy must be abnormal but may not yet be diagnostic meeting all of the IHSLT[1] criteria. For subsequent doses, all IHSLT criteria on biopsy must be met. [1] *The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: Evolution and current status (2005–2011) Berry et al JHLT 2011.* **Treatment or prevention of graft**	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. (A) Detail of the reason is to be provided. Acceptable contra-indication reasons include: i. Significant infection or sepsis ii. Potential for life threatening infection iii. Life threatening condition iv. Malignancy

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		rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient Conventional immunosuppressive therapy is contraindicated and the reason is provided.	v. Marrow suppression and cytopenia (A)
Review Criteria		**No review is required for one-off dosing.**	Given that treatment is mostly by multiple single doses, very limited outcome data is likely 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 after each exchange (Total maximum dose of 2.5g/Kg divided over 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 practice.

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		IVIg without plasma exchange (divided dose) 2 to 3.5g/kg in a divided dose **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.**	

POTENTIAL OPERATIONAL IMPACT			
No operational impact is anticipated.			
POTENTIAL IMPACT ON DEMAND			
Patient Numbers **& Usage** **2013-14**	**Patients treated:** Heart 18 patients Lung 76 patients Heart/lung 1 patient	No impact on demand is anticipated from introducing this structured approach. This change will provide the opportunity for data analysis and creating the potential for identification	

	Liver 2 patients Other 1 patient **Usage <1%**	of better practice.	
POTENTIAL IMPACT ON COST			
Current cost		**Anticipated reduction in cost, if any** **Marginal** = borderline or unchanged from current cost **Minor** = decrease by $500K - $1.99M from current cost **Major** = decrease $2M+ from current cost	**Marginal**
BIBLIOGRAPHY			
Berry et al JHLT 2011, IHSLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: Evolution and current status (2005–2011). Jordan, SC, Vo, A, Bunnapradist, S, et al 2003, 'Intravenous immune globulin treatment inhibits cross match positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients', *Transplantation*, vol. 76, no. 4, pp. 631–6.			
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