

Solid organ transplantation

Condition for which Ig has an emerging therapeutic role.

Specific Conditions	<ul style="list-style-type: none">• Kidney transplant• Liver and kidney transplant• Heart and kidney transplant• Pancreas and kidney transplant• Heart transplant• Lung transplant• Heart and lung transplant• Liver transplant• Heart and liver transplant• Other transplant
Indication for Ig Use	<ul style="list-style-type: none">• Immediate pre and/or post-transplant where donor specific antibody(s) prevent transplantation or threaten transplantation• Initial treatment of acute antibody mediated transplant rejection• Treatment of ongoing active antibody mediated transplant rejection• Ongoing desensitisation of patients to improve the likelihood of transplantation• Treatment or prevention of graft rejection where the use of conventional immunosuppressive therapies is contraindicated or poses a threat to the graft or patient
Level of Evidence	Clear evidence of benefit (Category 1)
Description and Diagnostic Criteria	<p>Transplant rejection occurs when a recipient’s immune system attacks a transplanted organ or tissue. Both cellular and humoral (antibody-mediated) effector mechanisms may play a role.</p> <p>Acute rejection occurs in 15 to 30 percent of organ transplants and may impact on long term graft survival. Over 90 percent of cases respond to steroids. Other anti-rejection treatments include anti-T cell antibody therapy, or if there is a component of AbMR, IVIg and plasma exchange may be required.</p> <p>In transplants that have been performed with a compatible cross match, antibody mediated rejection (AbMR) occurs in 5 to 10 percent of renal transplants and 10 to 20 percent of heart transplants. However, AbMR may be significantly higher in more sensitised recipients. AbMR is associated with an increased incidence of graft dysfunction, e.g. allograft nephropathy (kidney), coronary allograft vasculopathy (heart) and bronchiolitis obliterans (lung).</p> <p>Rejection is diagnosed histologically on tissue biopsy, with contributory information from clinical assessment, radiological and laboratory tests including determination of the presence and strength of antibodies against donor antigens.</p> <p>The diagnostic criteria (Banff Criteria) for AbMR in kidney transplants continues to evolve (Haas, 2014). In heart transplant, diagnostic criteria for AbMR must be consistent with the ISHLT Criteria (ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: Evolution and current status [2005–2011] Berry et al JHLT 2011).</p> <p>In non-kidney solid organ transplants, AbMR responds to IVIg with or without plasma exchange in more than 85 percent of patients.</p> <p>While the use of IVIg and plasma exchange forms the basis of treatment for acute AbMR, management of chronic AbMR is more challenging and there are currently very few controlled trials to guide clinicians on the optimal treatment of chronic AbMR.</p>
Justification for Evidence Category	<p>Kidney</p> <p>Desensitisation: The only randomised controlled trial (RCT) to date on desensitising patients awaiting kidney transplantation found that intravenous immunoglobulin (IVIg) was better than placebo in reducing allosensitisation in highly sensitised patients with end stage kidney disease (followed for two years after transplant), and that transplant rates were improved with IVIg therapy (Jordan et al 2004). Nonrandomised clinical observational studies suggest that a combination of plasmapheresis and low-dose IVIg is effective and provides a survival benefit for recipients (Montgomery 2011).</p> <p>Treatment of Acute Rejection: Multiple case series and some controlled trials have been reported in the literature indicating efficacy of IVIg in treating acute/active antibody mediated rejection, and it is</p>

recommended by a consensus conference (Takemoto et al 2004). There are no randomized controlled studies that have specifically studied the benefits of IVIg in acute AbMR, despite its common use in this context. Since 2008 there have been four non RCTs and three RCTs examining management of AbMR, all but one included IVIg and usually used both in the control and intervention arm of the trial (Lee 2016, Montgomery 2016, Choi 2016, Einecke 2016, Vigglitti 2016, Sautenet 2016, Zarkhin 2008).

Chronic antibody mediated rejection (AbMR): This is a challenging and evolving area, despite the significant adverse impact of chronic AbMR, there is limited literature to guide clinical practice and no widely accepted standard of care (Cooper 2014, Gupta 2014).

Solid organ - other than kidney

Ig therapy plays an important immunomodulatory role in incompatible organ transplantation with proven benefit (Level 1 evidence) for desensitisation of highly sensitised patients pre-transplant to improve transplant rates and clinical outcomes (Jordan, 2004). For desensitisation, trials have demonstrated improved outcomes when IVIg is used in association with rituximab and/or other immunosuppressant agents, and plasmapheresis.

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 one 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 five patients, but two patients later required further therapy with rituximab because of recurrent hemodynamic rejection. The role of Ig therapy in antibody mediated rejection is confirmed in a recent Scientific Statement of the American Heart Association (Colvin, 2015).

Diagnosis Requirements

A diagnosis must be made by a Transplantation Medicine Specialist.

Qualifying Criteria for Ig Therapy

Immediate pre and/or post-transplant where donor specific antibody(s) prevent transplantation or threaten transplantation

- ABO incompatible transplant, HLA antibody(s) (at least 500 MFI) or non-HLA antibody(s) threaten organ transplantation

Initial treatment of acute antibody mediated transplant rejection

- Presence of incompatible ABO blood group donor specific antibody(s), donor specific HLA antibody(s) (at least 500 MFI) and/or donor specific non-HLA antibody(s)
- AND
- Organ biopsy demonstrates antibody mediated rejection according to Banff criteria (Haas et al, 2014) or ISHLT or other evidence of antibody-mediated rejection (for example, other applicable scoring system if available)

OR

- Presence of incompatible ABO blood group donor specific antibody(s), donor specific HLA antibody(s) (at least 500 MFI) or donor specific non-HLA antibody(s)
- AND
- Current clinical and laboratory evidence of graft dysfunction where a biopsy is not available

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)

	<div>Treatment of ongoing active antibody mediated transplant rejection</div> <div> <ul style="list-style-type: none"> Ongoing antibody mediated rejection as demonstrated by biopsy in accordance with BANFF, ISHLT or other evidence of antibody-mediated rejection (for example, other applicable scoring system, if available) <p>Review by a transplantation specialist is required within two months of treatment to determine whether the patient has responded. If no response, Ig therapy should be ceased. Subsequent review by a transplantation specialist is required every four months where cessation of Ig therapy should be considered.</p> <p>Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.</p> </div> <div>Ongoing desensitisation of patients to improve the likelihood of transplantation</div> <div> <ul style="list-style-type: none"> Highly sensitised patient and/or known presence of high level donor specific antibody(s), resulting in a low likelihood of receiving an organ <p>AND</p> <ul style="list-style-type: none"> Circumstances indicate that the likelihood of receiving an organ is very low <p>Review by a transplantation specialist is required within two months of treatment to determine whether the patient has responded. If no response, Ig therapy should be ceased. Subsequent review by a transplantation specialist is required every four months where cessation of Ig therapy should be considered.</p> <p>Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.</p> </div> <div>Treatment or prevention of graft rejection where the use of conventional immunosuppressive therapies is contraindicated or poses a threat to the graft or patient</div> <div> <ul style="list-style-type: none"> Conventional immunosuppressive therapy is contraindicated and a reason is provided <p>AND</p> <ul style="list-style-type: none"> A transplant has been received <p>AND</p> <ul style="list-style-type: none"> The patient has previously responded to Ig therapy <p>OR</p> <ul style="list-style-type: none"> The patient has never received Ig therapy </div>
<div>Review Criteria for Assessing the Effectiveness of Ig Use</div>	<div>Immediate pre and/or post-transplant where donor specific antibody(s) prevent transplantation or threaten transplantation</div> <div> <p>Review is not mandated for this indication however the following criteria may be useful in assessing the response to Ig therapy:</p> <ul style="list-style-type: none"> Reduction in antibody level <p>AND</p> <ul style="list-style-type: none"> Transplantation proceeds </div>

Initial treatment of acute antibody mediated transplant rejection

Review is not mandated for this indication however the following criteria may be useful in assessing response to Ig therapy:

- Reduction in antibody level
- AND
- Reduction in evidence of graft rejection on biopsy
- AND
- Improvement in graft function

Treatment of ongoing active antibody mediated transplant rejection

Review by a transplantation specialist is required within two months of treatment to determine whether the patient has responded. If no response, Ig therapy should be ceased. Subsequent review by a transplantation specialist is required every four months where cessation of Ig therapy should be considered.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy can be assessed by:

On review of the initial authorisation period

- Improvement in graft function or evidence of rejection on biopsy (if performed) compared to the qualifying assessment
- AND
- Evidence of response to Ig therapy as compared to the qualifying assessment

On review of a continuing authorisation period

- Improvement in graft function or evidence of rejection on biopsy (if performed) compared to the previous assessment
- AND
- Evidence of response to Ig therapy as compared to the previous assessment
- AND
- Consideration of cessation of Ig therapy

Ongoing desensitisation of patients to improve the likelihood of transplantation

Review, ideally undertaken by a transplantation specialist, is required within two months of treatment to determine whether the patient has responded. If no response, Ig therapy should be ceased. Subsequent review by a transplantation specialist is required every four months where cessation of Ig therapy should be considered.

Patients who have received an organ are not eligible for Ig under this indication but may be eligible under a different indication.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy can be assessed by:

- Reduction in the level of HLA or other donor specific antibodies as demonstrated by a decrease in the MFI or a reduced antibody reactivity or reduction in the number of Non-HLA antibodies compared to the qualifying assessment

AND

- Specific circumstances exist to justify treatment for a further course
- AND
- The patient has not received an organ

Treatment or prevention of graft rejection where the use of conventional immunosuppressive therapies is contraindicated or poses a threat to the graft or patient

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.

- Improvement in evidence of biopsy and graft function compared to the qualifying assessment
AND
- Evidence of response to Ig therapy as compared to the qualifying assessment

OR

- Ig therapy was for prevention of graft rejection

Dose

Immediate pre and/or post-transplant where donor specific antibody(s) prevent transplantation or threaten transplantation

- **One-off dose (IVIg)** - Up to 2 g/kg to a maximum of 140g which may be given as a divided dose.
- **Repeated Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in separate doses up to a total maximum dose of 2g/Kg/8 week period.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Initial treatment of acute antibody mediated transplant rejection

- **One-off dose (IVIg)** - Up to 2 g/kg to a maximum of 140 g which may be given as a divided dose.
- **Recurrent Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/8 week period.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Treatment of ongoing active antibody mediated transplant rejection

- **Ig with or without plasma exchange (IVIg)** - 0.1 to 1.0 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/4 week period.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Ongoing desensitisation of patients to improve the likelihood of transplantation

- **Maintenance Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/4 week period.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Treatment or prevention of graft rejection where the use of conventional immunosuppressive therapies is contraindicated or poses a threat to the graft or patient

- **Recurrent Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in divided doses up to a total of 2g/Kg in a 4 week period.

- **Single divided dose (IVIg)** - Up to 2 g/kg as a single dose.

Therapy should be reviewed and cessation considered if an improvement has not been achieved after two consecutive authorisations.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

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