Kidney transplantation

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	• Kidney transplantation pre-transplant • Kidney transplantation post-transplant
Indication for IVIg Use	• Pre-transplantation where an antibody or antibodies prevent transplantation (donor-specific anti-human leukocyte antigen [HLA] antibody/ies and/or anti-blood group antibody). • Post-transplantation to treat biopsy proven cellular rejection unresponsive to steroids - or acute antibody mediated rejection. • For prevention and/or treatment of rejection where other therapies are contraindicated or pose a threat to the graft or patient.
Level of Evidence	Clear evidence of benefit (Category 1)
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 renal transplants and is responsive to steroids in more than 90% of cases. When rejection is steroid resistant, intravenous immunoglobulin (IVIg) is a safer therapy than anti-T cell antibody therapy, with equal efficacy. Antibody-mediated rejection (AbMR) occurs 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.
Justification for Evidence Category	A randomised controlled trial (RCT) enrolling adult patients with end-stage renal disease (ESRD) who were highly sensitised to human leucocyte antigen (HLA) 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 (2003) 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 that IVIg generated fewer side effects (Casadei et al 2001).
Qualifying Criteria for IVIg Therapy	Pre-transplantation where an antibody or antibodies prevent transplantation (donor-specific anti-human leukocyte antigen [HLA] antibody/ies and/or anti-blood group antibody). • Antibodies prevent organ transplantation. Post-transplantation to treat biopsy proven cellular rejection unresponsive to steroids - or acute antibody mediated rejection. • Clinical and/or laboratory evidence of graft dysfunction. AND • Biopsy-proven cellular rejection unresponsive to steroids. OR • Acute antibody-mediated rejection. OR • There is a high clinical suspicion of antibody mediated rejection and evidence is not yet available (one-off request in early period of acute rejection) For prevention and/or treatment of rejection where other therapies are contraindicated or pose a threat to the graft or patient. • Conventional immunosuppressive therapy is contraindicated.

Review Criteria for Assessing the Effectiveness of IVIg Use

Pre-transplantation where an antibody or antibodies prevent transplantation (donor-specific anti-human leukocyte antigen [HLA] antibody/ies and/or anti-blood group antibody).

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

Clinical effectiveness of Ig therapy may be demonstrated by:

- Laboratory monitoring of anti-HLA and/or anti-blood group antibody responses.

Post-transplantation to treat biopsy proven cellular rejection unresponsive to steroids - or acute antibody mediated rejection.

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

Clinical effectiveness of Ig therapy may be demonstrated by:

- Reversal of clinical graft dysfunction.

  AND
- Laboratory monitoring of anti-HLA and/or anti-blood group antibody responses.

  AND
- Duration of graft and patient survival.

For prevention and/or treatment of rejection where other therapies are contraindicated or pose 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 therapy.

Clinical effectiveness of Ig therapy may be demonstrated by:

- Reversal of graft dysfunction.

  AND
- Duration of graft and patient survival.

Dose

Pre-transplantation where an antibody or antibodies prevent transplantation (donor-specific anti-human leukocyte antigen [HLA] antibody/ies and/or anti-blood group antibody).

- **IVIg with plasma exchange** - 0.1 to 0.5 g/kg after each exchange (up to a total maximum dose of 2.5g/kg)
- **IVIg without plasma exchange (single dose)** - up to 2 g/kg, to a maximum of 140 g as a single dose.
- **IVIg without plasma exchange (divided dose)** - 2 to 3.5 g/kg in a divided dose.

When IVIg is used alone, further doses may be warranted two to four weeks after initial therapy, depending on clinical response and/or biopsy findings.

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.

Post-transplantation to treat biopsy proven cellular rejection unresponsive to steroids - or acute antibody mediated rejection.

- **IVIg with plasma exchange** - 0.1 to 0.5 g/kg after each exchange (up to a total maximum dose of 2.5g/kg).
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For prevention and/or treatment of rejection where other therapies are contraindicated or pose a threat to the graft or patient.

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