Solid organ transplantation (other than kidney)

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	• Solid organ - heart • Solid organ - heart/lung • Solid organ - lung • Solid organ - liver • Solid organ - other
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 acute antibody-mediated rejection with clinical evidence of graft dysfuction. • Treatment or prevention of graft rejection, where conventional immunosuppressive therapy is contraindicated or will place the patient or the graft at risk.
Level of Evidence	Insufficient data (Category 4a)
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. 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 (ISHLT) criteria (Berry et al 2011).
Justification for Evidence Category	Jordan et al (2003) 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 intravenous immunoglobulin (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 patients, but 2 patients later required further therapy with rituximab because of recurrent hemodynamic rejection.

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 acute antibody-mediated rejection with clinical evidence of graft dysfuction.

- Clinical and/or laboratory evidence of graft dysfunction.

AND

- Acute antibody-mediated rejection.

  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).

Treatment or prevention of graft rejection, where conventional immunosuppressive therapy is contraindicated or will place the patient or the graft at risk.

- 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 anti-blood group antibody responses.

Post-transplantation to treat acute antibody-mediated rejection with clinical evidence of graft dysfuction.

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 anti-blood group antibody responses.

  AND
- Duration of graft and patient survival.

Treatment or prevention of graft rejection, where conventional immunosuppressive therapy is contraindicated or will place the patient or the graft at risk.

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
- 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 (total maximum dose of 2.0g/kg across divided doses, monthly)
- **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)** - 2–3.5 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 achives 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 acute antibody-mediated rejection with clinical evidence of graft dysfuction.

- **IVIg with plasma exchange** - 0.1 to 0.5 g/kg after each exchange, up to a maximum total 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.

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Treatment or prevention of graft rejection, where conventional immunosuppressive therapy is contraindicated or will place the patient or the graft at risk.

- **IVIg with plasma exchange** - 0.1 to 0.5 g/kg after each exchange, up to a maximum total 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.

Bibliography

Berry, GJ, Angelini, A, Burke, MM, et al 2011, 'The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: evolution and current status (2005–2011)', *Journal of Heart and lung Transplantation,* vol. 30, no. 6, pp. 601–11.

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