Autoimmune haemolytic anaemia (AIHA)

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	• Autoimmune haemolytic anaemia • Evans Syndrome with significant AIHA
Indication for IVIg Use	• To reduce haemolysis in patients with AIHA not responding to corticosteroid therapy • Intermittent therapy for AIHA in patients unsuitable for splenectomy or immunosuppression • Maintenance therapy for AIHA in patients unsuitable for splenectomy or immunosuppression
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	Autoimmune haemolytic anaemia (AIHA) is a rare but serious autoimmune disease in which an individual's antibodies recognise antigens on their own red blood cells. AIHA presents as an acute or chronic anaemia characterised by the occurrence of biochemical parameters of red cell destruction associated with a positive direct antiglobulin test indicating the presence of antibodies and/or complement on the red cell surface. It may be secondary to a number of underlying disorders or drugs. Evans syndrome is a rare but serious autoimmune disease defined by the simultaneous or sequential occurrence of AIHA and immune thrombocytopenia purpura (ITP) without underlying aetiology. As such, it is a diagnosis of exclusion and other disorders, such as collagen vascular diseases, especially systemic lupus erythematosus (SLE) and scleroderma should be ruled out. The 2005 review by Norton and Roberts provided perspective on diagnosis, clinical features and management. **Investigations** A full blood count will confirm the presence of anaemia. A peripheral blood smear may reveal evidence of spherocytes along with polychromasia due to reticulocytosis. A direct antiglobulin test is usually positive, the serum lactate dehydrogenase is raised, and there is a reduction in serum haptoglobin. **Prognosis** The prognosis of AIHA is good in most cases although severe refractory AIHA can cause cardio-respiratory problems because of severe anaemia, especially in adults. **Standard therapy** Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.
Justification for Evidence Category	An analysis of 73 patients with autoimmune haemolytic anaemia (AIHA) in 1993 based on three pilot studies and a literature review showed a 40 percent response to IVIg given together with corticosteroids. A lower initial haemoglobin concentration and hepatomegaly were positive correlates of response. Several small case series have suggested a benefit for IVIg in AIHA associated with lymphoproliferative diseases, especially chronic lymphocytic leukaemia (CLL). On the basis of these findings, IVIg is not supported as standard therapy for AIHA, only in cases refractory to conventional corticosteroid therapy, as a temporising measure before splenectomy or as maintenance therapy where splenectomy or

	immunosuppression are not appropriate. A 2005 review on the management of Evans syndrome, based on Massachusetts Hospital data and a literature review, showed a transient response in all patients unless IVIg was given every three weeks (Norton and Roberts 2006). The review concluded that the data supported a role for IVIg in first-line therapy. It was not clear whether it was important for steroids to be given at the same time, although this is common practice. A total dose of 2 g/kg in divided doses appeared to be sufficient. The review also stated that there might be a role for IVIg in preference to steroids in the acute setting in very young children.
Diagnosis Requirements	A diagnosis must be made by a Haematologist, Paediatrician or a General Medicine Physician.
Qualifying Criteria for IVIg Therapy	To reduce haemolysis in patients with AIHA not responding to corticosteroid therapy • Symptomatic or severe disease with current haemoglobin of less than 60g/L (except where comorbidities exist that would influence the tolerance of anaemia) AND • Haemolysis persists after at least 14 days of conventional corticosteroid therapy OR • Corticosteroid therapy is contraindicated OR • As a temporising measure before splenectomy Intermittent therapy for AIHA in patients unsuitable for splenectomy or immunosuppression • Symptomatic or severe disease with current haemoglobin of less than 60g/L (except where significant comorbidities exist that would influence the tolerance of anaemia AND • Haemolysis persists after at least 14 days of conventional corticosteroid therapy OR • Corticosteroid therapy is contraindicated. AND • Splenectomy is contraindicated AND • Immunosuppressant therapy is contraindicated

	Maintenance therapy for AIHA in patients unsuitable for splenectomy or immunosuppression • Symptomatic or severe disease (Hb<60g/L, except in patients with comorbidities) requiring ongoing transfusion support for at least two months. AND • Haemolysis persists after at least 14 days of conventional corticosteroid therapy OR • Corticosteroid therapy is contraindicated AND • Splenectomy is contraindicated AND • Immunosuppressant therapy is contraindicated Review by a haematologist, general physician or paediatrician is required six monthly. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. Cessation of Ig treatment should be considered at each review.
Exclusion Criteria	Adult with Evans syndrome where the predominant feature is ITP - see Immune thrombocytopenic purpura (ITP) — adult Child with Evans syndrome where the predominant feature is ITP - see Immune thrombocytopenic purpura (ITP) — in children 15 years and younger
Review Criteria for Assessing the Effectiveness of IVIg Use	To reduce haemolysis in patients with AIHA not responding to corticosteroid therapy **Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Resolution of haemolytic anaemia (rising haemoglobin concentrations, diminished transfusion requirement) AND • Clinical improvement in symptoms and signs Intermittent therapy for AIHA in patients unsuitable for splenectomy or immunosuppression **Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Resolution of haemolytic anaemia (rising haemoglobin concentrations, diminished transfusion requirement) AND • Clinical improvement in symptoms and signs

Maintenance therapy for AIHA in patients unsuitable for splenectomy or immunosuppression

Review by a haematologist, general physician or paediatrician is required six monthly. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. Cessation of Ig treatment should be considered at each review.

Clinical effectiveness of Ig therapy can be assessed by:

On review of the initial authorisation period

- Haemolysis is unresolved and patient remains transfusion dependant and symptomatic

  AND

- Contraindication reasons for splenectomy and immunosuppressant therapy remain

  AND

- A trial off Ig therapy is planned or a valid reason is provided as to why a trial is not planned or is contraindicated

On review of a continuing authorisation period

- Haemolysis is unresolved and patient remains transfusion dependant and symptomatic

AND

- Contraindication reasons for splenectomy and immunosuppressant therapy remain

AND

- A trial off Ig therapy is planned or a valid reason is provided as to why a trial is not planned or is contraindicated.

Dose

To reduce haemolysis in patients with AIHA not responding to corticosteroid therapy

- **Dose** - Recommended dose is 0.8-2g/Kg as a single dose or divided dose. An additional dose may be allowed 72 hours after the first dose, up to a total of 2g/kg.

Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments, while anti-CD20 antibodies have shown promise in individual cases of refractory disease.

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.

Intermittent therapy for AIHA in patients unsuitable for splenectomy or immunosuppression

- **Dose** - 0.8-2g /kg as a single dose or divided dose. An additional dose may be allowed 72 hours after the first dose, up to a total of 2g/kg.

Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second-line treatments, while anti-CD20 antibodies have shown promise in individual cases of refractory disease.

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.

Maintenance therapy for AIHA in patients unsuitable for splenectomy or immunosuppression

- **Maintenance Dose** - 0.8-2g/kg as a single dose or divided dose 4 to 6 weekly.

Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.

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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