Acquired haemophilia and congenital haemophilia with inhibitors (Coagulation factor inhibitors)

Version: 3.0
Published: 20 October 2018

Condition for which IVIg use is in exceptional circumstances only

Specific Conditions	• Congenital haemophilia A with acquired factor VIII inhibitor • Congenital haemophilia B with acquired factor IX inhibitor • Acquired haemophilia A • Acquired haemophilia B • Acquired von Willebrand syndrome • Acquired bleeding disorder, other coagulation factors (Prothrombin, factor V, factor VII, factor X, factor XI, and factor XIII)
Indication for IVIg Use	• As part of Malmo tolerisation protocol replacement following immunoadsorption • As adjunct therapy in the treatment of acquired coagulation factor inhibitors • Treatment of active bleeding in acquired von Willebrand disease associated with an IgG paraprotein
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	Inhibitors to coagulation factors are antibodies that can interfere with the function of specific clotting proteins including factor VIII, factor IX and less commonly, other coagulation factors. Inhibitors can be allo-antibodies as occurs in congenital haemophilia in response to infused product, or auto-antibodies as occurs in acquired haemophilia which may be seen in the setting of other autoimmune disease, malignancy, post-partum or in response to certain drugs. The incidence of acquired cases is very low and usually respond to steroids (first-line) and IVIg would only usually be considered in the setting of ongoing bleeding. Patients may present with abnormal bleeding which can be severe and life threatening, and in these circumstances treatment is best co-ordinated in association with haemophilia treatment centres. The presence and level of inhibitor should be confirmed where possible by a factor specific Bethesda assay. Where laboratory confirmation is not able to be easily performed, as in acquired Von Willebrand disease, significantly reduced response to infused factor concentrate or demonstration of new onset of reduced clotting factors levels can be used to make the diagnosis.
Justification for Evidence Category	Intravenous immunoglobulin (IVIg) has a role as part of a second-line immune tolerance protocol involving immunoadsorption and immunoglobulin replacement, in addition to immunosuppression and factor replacement, the Malmo protocol (Nilsson et al, 1988 and Berntorp et al, 2000 and Franchini & Lippi, 2008 and Zeitler et al, 1991). There is evidence for the beneficial effect of this protocol in patients with: • Congenital haemophilia A with acquired factor VIII inhibitors • Congenital haemophilia B with acquired factor IX inhibitors • Acquired haemophilia A IVIg has an accepted role in the reduction of bleeding in patients with acquired von Willebrand syndrome and IgG paraproteins (Collins et al, 2013). IVIg has an uncertain role in the reduction of bleeding in patients with other

	acquired bleeding disorders associated with the development of specific coagulation factor inhibitors. There is conflicting data, and conflicting recommendations. There is no role for IVIg as first-line, or as monotherapy in the reduction of bleeding in these disorders. However, IVIg may serve a limited but supportive role in managing patients who are bleeding, or at high risk of bleeding, with limited response to first-line immunosuppression. (Collins et al, 2013 and Guglielmone et al, 2011). In all of these circumstances, advice regarding the management of patients with acquired inhibitors and the use of Ig can be be accessed from a local Haemophilia Treatment Centre. Patients with Acquired von Willebrand syndrome with IgM autoantibodies/paraprotein may be better amenable to plasmapheresis, but local guidelines should apply. Evidence suggests these patients do not respond to Ig therapy. (Federici et al, 1998 and Federici, 2005 and Collins et al, 2013).
Diagnosis Requirements	A diagnosis must be made by a Haematologist.
Qualifying Criteria for IVIg Therapy	As part of Malmo tolerisation protocol replacement following immunoadsorption • Congenital haemophilia A or B with inhibitors, or acquired haemophilia A AND • Unresponsive to first line treatment by tolerisation including steroids and immunosuppressant agents OR • Immunosuppressant therapy is contraindicated AND • Ig prescribed as part of the Malmo protocol in consultation with a Haemophilia Treatment Centre Review by a Haematologist is required within six months of treatment to determine whether the patient has responded, and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. As adjunct therapy in the treatment of acquired coagulation factor inhibitors • Presence of acquired coagulation factor inhibitors with evidence of bleeding or a risk of bleeding is determined AND • Unresponsive to first line treatment including steroids and immunosuppressant agents OR • Immunosuppressant therapy is contraindicated

	Treatment of active bleeding in acquired von Willebrand disease associated with an IgG paraprotein • Evidence of acquired von Willebrand disease with evidence of bleeding or risk of bleeding AND • No other indication exists for systemic chemotherapy or immunosuppressant therapy AND • Ig therapy is given in consultation with a Haemophilia Treatment Centre Review by a Haematologist is required within six months of treatment to determine whether the patient has responded, and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.
Exclusion Criteria	Acquired von Willebrand syndrome with IgM autoantibodies/paraprotein
Review Criteria for Assessing the Effectiveness of IVIg Use	As part of Malmo tolerisation protocol replacement following immunoadsorption Review by a Haematologist is required within six months of treatment to determine whether the patient has responded, and six monthly thereafter. 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** • Reduction in bleeding symptoms or in the risk of bleeding AND • Reduction in or absence of inhibitors **On review of a continuing authorisation period** • Reduction in bleeding symptoms or the risk of bleeding AND • Reduction in or absence of inhibitors

As adjunct therapy in the treatment of acquired coagulation factor inhibitors

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

- Reduction in bleeding symptoms, or risk of bleeding

AND

- Reduction in or absence of inhibitor levels

Treatment of active bleeding in acquired von Willebrand disease associated with an IgG paraprotein

Review by a Haematologist is required within six months of treatment to determine whether the patient has responded, and six monthly thereafter.

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

- Reduction in bleeding symptoms or risk of bleeding

On review of a continuing authorisation period

- Reduction in bleeding symptoms or risk of bleeding

Dose

As part of Malmo tolerisation protocol replacement following immunoadsorption

- **Induction Dose** - 1 g/kg as a divided dose over 3 days.
- **Maintenance Dose** - 1 g/kg in divided dose over 3 days, weekly as part of the Malmo protocol.

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.

As adjunct therapy in the treatment of acquired coagulation factor inhibitors

- **Induction Dose** - Up to 2 g/kg as a single or divided dose.
  Should be given in combination with immunosuppressant therapy from three to six weekly.

Up to two additional doses may be requested. Please confirm patients have responded and are receiving concurrent immunosuppressant therapy. The two additional doses can be authorised at three to six weekly intervals.

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 active bleeding in acquired von Willebrand disease associated with an IgG paraprotein

- **Induction Dose** - 2g/kg as a divided dose over 2 to 5 days.
- **Maintenance Dose** - 1g/kg three to four weekly.

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.

Bibliography

Batorova, A, Morongova, A, Tagariello G, Jankovicova, D, et al 2013, 'Challenges in the management of hemophilia B with inhibitor', *Semin Thrombosis and Hemostasis,* vol. 39, no. 7, pp. 767-71. https://www.ncbi.nlm.nih.gov/pubmed/24022802

Berntorp, E, Astermark, J & Carlborg, E 2000, 'Immune tolerance induction and the treatment of hemophilia. Malmö protocol update', *Haematologica*, vol. 85, suppl 10, pp. 48-50. https://www.ncbi.nlm.nih.gov/pubmed/11187871

Collins, PW, Hirsch, S, Baglin, TP, et al 2007, 'Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation', *Blood*, vol. 109, no. 5, pp. 1870-7. https://www.ncbi.nlm.nih.gov/pubmed/17047148

Collins, PW, Chalmers, E, Hart, D, et al 2013, 'Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO', *British Journal of Haematology*, vol. 162, no. 6, pp. 758–73. https://www.ncbi.nlm.nih.gov/pubmed/23889317

Federici, AB, Stabile, F, Castaman, G, et al 1998, 'Treatment of acquired von Willebrand syndrome in patients with

monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches', *Blood*, vol. 92, no. 8, pp. 2707-11. https://www.ncbi.nlm.nih.gov/pubmed/9763553

Federici, AB 2005, 'Use of intravenous immunoglobulin in patients with acquired von Willebrand syndrome', *Human Immunology*, vol. 66, no. 4, pp. 422-30. https://www.ncbi.nlm.nih.gov/pubmed/15866707

Franchini, M & Lippi, G 2008, 'Acquired factor VIII inhibitors', *Blood*, vol. 112, pp. 250-255. http://www.bloodjournal.org/content/112/2/250?sso-checked=true

Guglielmone, H, Jarchum, G & Minoldo, S 2011, 'Successful treatment with intravenous immunoglobulin (IVIg) in a patient with an acquired factor V inhibitor after liver transplantation', *Thrombosis and Haemostasis*, vol. 106, no 5, pp. 985-6. https://www.ncbi.nlm.nih.gov/pubmed/21901236

Hay, CR, Brown, S, Collins, PW, et al 2006, 'The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation', *British Journal of Haematology*, vol. 133, no. 6, pp. 591–605. https://www.ncbi.nlm.nih.gov/pubmed/16704433

Mazzucconi, MG, Peraino, M, Bizzoni, L, et al 1999, 'Acquired inhibitor against factor IX in a child: successful treatment with high-dose immunoglobulin and dexamethasone', *Haemophilia*, vol. 5, no. 2, pp. 132–4. https://www.ncbi.nlm.nih.gov/pubmed/10215963

Nilsson, IM, Berntorp, E & Zettervall, O 1988, 'Induction of immune tolerance in patients with hemophilia and antibodies to factor VIII by combined treatment with intravenous IgG, cyclophosphamide, and factor VIII', *New England Journal of Medicine*, vol. 318, no. 15, pp. 947-50. https://www.ncbi.nlm.nih.gov/pubmed/3127711

Schwartz, RS, Gabriel, DA, Aledort, LM, et al 1995, 'A prospective study of treatment of acquired (autoimmune) factor VIII inhibitors with high-dose intravenous gammaglobulin', *Blood*, vol. 86, no. 2, pp. 797–804. https://www.ncbi.nlm.nih.gov/pubmed/7606010

Sultan, Y, Kazatchkine, MD, Nydehgger, U, et al 1991, 'Intravenous immunoglobulin in the treatment of spontaneously acquired factor VIII:C inhibitors', *American Journal of Medicine*, vol. 91, no. 5A, pp. 35S-39S. https://www.ncbi.nlm.nih.gov/pubmed/1746595

Tiede, A, Rand, JH, Budde, U, et al 2011, 'How I treat the acquired von Willebrand syndrome', *Blood, vol.* 117, no. 25, pp.6777-85. https://www.ncbi.nlm.nih.gov/pubmed/21540459

UK Department of Health 2011, 'Clinical Guidelines for Immunoglobulin Use: Second Edition Update', Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.pdf

UK Department of Health 2011, 'Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster', Available from: https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster_v4_February2016.pdf

Zeitler, H, Ulrich-Merzenich, G, Hess, L, et al 2005, 'Treatment of acquired hemophilia by the Bonn-Malmo Protocol: documentation of an in vivo immunomodulating concept', *Blood*, vol. 105, no.6, pp. 2287-93. https://www.ncbi.nlm.nih.gov/pubmed/15542586

Generated on: 4 April 2019