HSE Guidelines for Immunoglobulin use in Neurological Conditions

This document is intended for use by healthcare professionals only.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

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Immunoglobulin Guidelines (IG)

These IG guidelines have been reviewed by a group of prescribing physicians and healthcare professionals who are members of the National Clinical Programme for Neurology. The guidelines are designed to standardise practice and support the implementation of treatment pathways for neurology patients in Ireland.

Contents

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Introduction

The Intravenous Immunoglobulin (IVIG) working group was set up by the National Clinical Programme for Neurology to establish criteria for the use of immunoglobulins (IG) for neurological conditions. IVIG is increasingly prescribed for unlicensed conditions where there is limited evidence to support use and IVIG is sometimes continued in circumstances where the benefit of treatment is not clear. The objective of these guidelines is to provide evidence-based recommendations on the effective, efficient, and clinically appropriate use of IVIG and to provide review criteria for demonstrating the effectiveness of IVIG use. The guideline aims to demonstrate stewardship for reserving IVIG use for indications with high levels of evidence.

Neurology is a therapeutic area that is highly complex and the evidence to support practice is continually evolving and maturing. In an acute setting individual consultants make clinical decisions based on individual patient needs where clinical judgement determines reasonable likelihood of therapeutic benefit. In the acute setting, it is recommended that the rationale for IVIG treatment is documented in the patient's notes in accordance with good clinical practice.

In the event of empiric use of IVIG in the chronic setting, start and stop criteria should be discussed with the patient and/or caregiver and documented within the patient's notes.

Prescribing Principals

- Intravenous IG (IVIG) treatment is considered after exploring all other safe, effective, and affordable alternative therapies.
- When IVIG is used, the lowest dose for the shortest duration required to achieve the desired outcome should be chosen.
- For ongoing therapy, the achievement of pre-defined, measurable clinical outcomes is a requirement; IVIG should not be continued in patients with no demonstrable benefit.

Target population for this guideline:

Adult patients diagnosed with a neurological condition in an HSE acute hospital. The use of IG requires understanding of the diagnosis and pathophysiology of the disorder being treated. This includes monitoring and measuring outcomes to inform further treatment. A review by an appropriate specialist familiar with the product should occur prior to the initiation of IG therapy, whenever possible. Ongoing use of IG for chronic conditions should be done primarily by specialists with expertise in the particular disorder being treated, or in partnership with them.

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Efficacy Outcomes to Assess Treatment Effects

Objective measures of effectiveness should be established at the onset of treatment and agreed upon by prescriber and patient. If these measures have not been met after a defined period of time, IVIG treatment should be stopped.

This guideline provides clinically relevant and biologically plausible efficacy outcomes to be measured in all indications. It is expected that all indications will have efficacy parameters defined and monitored on a case by case basis. Efficacy outcomes are expected to play an important role in the decision-making process for patients in whom continuation of immunoglobulin treatment is requested beyond the short- and long-term durations defined in this guideline. Clinicians should be able to provide details of the proposed assessment score(s). The appropriate score(s) is/are determined at baseline prior to initiation of therapy and is/are based on the individual patient's presentation. Appropriate scores are listed for each presentation in table below.

Duration of Treatment

In this document, short term treatment is defined as

- Three prescribed doses of up to 2 g/kg, given at appropriate clinical intervals.
- Less than or equal to 3 months
- The treatment episode ends at 3 months.

Long term treatment is any course of IVIG greater than or equal to 3 months. It is recommended that all patients on long term courses of IVIG should have a thorough review carried out at regular intervals, ideally every 6 months though this may not always be feasible in clinical practice. The review should include assessing the patient against the agreed objective measures of clinical efficacy that were pre-defined at treatment initiation. If the degree of improvement does not meet the criteria defined then treatment with IVIG should be stopped. If the patient is stable then the dose and frequency of treatment should be titrated to the lowest effective dose and longest interval between doses that maintains stability. IVIG requirement should also be assessed, it is a valid clinical decision to stop IVIG treatment for trial period and reassess.

Monitoring of patients receiving long term IVIG should also include full blood count, liver function tests and urea and electrolytes.

Funding for Treatment

Patients within the public health system will be funded for their treatment with IVIG by the Health Service Executive (HSE).

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Dosing

Unless otherwise indicated, use adjusted body weight for dosing calculations in overweight or obese adults as follows.

> **Dosing Weight** is an *adjusted* body weight (of overweight or obese patients):
> Dosing Weight = IBW + [0.4 x (Actual - IBW)]
> Note: If actual body weight is less than IBW, then Dosing Weight = actual body weight.
>
> **Ideal Body Weight (IBW)**, Devine formula is:
> IBW (male) = 50.0 kg + 2.3 kg (each inch over 5 feet)
> IBW (female) = 45.5 kg + 2.3 kg (each inch over 5 feet)

Table 1: Criteria for the use of Immune Globulin in Neurological Indications

Approved use: Established therapeutic role with clear evidence of benefit

Exceptional use: Emerging therapeutic role with evidence of probable benefit and more research needed. Treatment should be discussed with a specialist or Key Opinion Leader whenever possible on a case by case basis

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Indication	Acute 'Rescue' Short Term Use	Long term Maintenance use	Start Criteria	Stop Criteria	Dose	Monitoring	Potential Outcome Measures	Alternative Treatment
Approved Use								
Guillain-Barré Syndrome & Guillain-Barré Syndrome variants	Yes	No	Diagnosis of GBS or variant in hospital AND significant disability (Hughes Disability Score* Grade 3 or above. Able to walk 5m with an aid) OR progression of disease. Treatment should be started within two weeks of symptom onset	Course completion	2 g/kg adjusted body weight divided over 2 to 5 days. A second course of IVIG may be considered in patients with clearly demonstrated secondary deterioration, after assessment by a neurologist.	Improvement in disability at four weeks after IVIG treatment measured using the Hughes disability score	Physical & Clinical examination Hughes Disability Score GBS score	Plasma Exchange
Chronic inflammatory demyelinating polyneuropathy Including Ganglionopathies and paraprotein associated demyelinating neuropathy (IgA, IgG, IgM), Nodal/ Para-nodal antibodies	Yes	Yes	Rapid progression, significant disability, functional impairment or compromised walking	Review after 6 months & if clinical effectiveness has not been achieved or sustained & there has not been an improvement on the predefined disease measurement score then discontinue IVIG. *IVIG could be stopped for a trial period*	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days. **Maintenance therapy:** 0.5 -2kg every 4 to 8 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy.	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment, in consultation with a neurologist. For stable patients, these measures should be assessed, in consultation with a neurologist, no later than 6 months after initiation of long-term treatment and at least biannually thereafter.	Physical & Clinical examination Imaging results ONLS INCAT MRC Timed walk.	IVIG is first line treatment. Concomitant therapy with immuno-suppressants may be required in refractory cases.
Multifocal Motor Neuropathy (MMN)	No	Yes	Diagnosis should be made by a neuromuscular specialist, as very specific electrodiagnostic expertise is required	Review after 6 months & if clinical effectiveness has not been achieved or sustained & there has not been an improvement on the predefined disease measurement score then discontinue IVIG. *IVIG could be stopped for a trial period*	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days. **Maintenance therapy:** 0.4 - 2g/kg every 2 to 6 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy.	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least biannually thereafter.	Physical & Clinical examination ONLS Physical Examination Power Score Timed walk	IVIG is first line treatment.

Indication	Acute 'Rescue' Short Term Use	Long term Maintenance use	Start Criteria	Stop Criteria	Dose	Monitoring	Potential Outcome Measures	Alternative Treatment
Myasthenia Gravis	*Yes*	Yes (individual patients can be considered for maintenance treatment)	Diagnosis of acute exacerbation (myasthenic crisis) or before surgery and/or thymectomy. Maintenance therapy for moderate to severe generalized MG when other treatments are ineffective or have caused intolerable side effects	Review after 6 months & if clinical effectiveness has not been achieved or sustained & there has not been an improvement on the predefined disease measurement score then discontinue IVIG. *IVIG could be stopped for a trial period*	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days. **Maintenance therapy:** 0.4 - 1g/kg every 4 to 6 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy.	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least biannually thereafter.	Physical & Clinical examination MGC score	Alternative to IVIG during acute crisis: plasma exchange First line maintenance: Corticosteroids, other immunosuppressive-agent
Stiff Person Syndrome	Yes	Yes	IVIG is recommended for treatment of significant functional impairment in patients who have stiff person syndrome, verified in consultation with a neurologist	Review after 6 months & if clinical effectiveness has not been achieved or sustained & there has not been an improvement on the predefined disease measurement score then discontinue IVIG. *IVIG could be stopped for a trial period*	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days. **Maintenance therapy:** 1-2g/kg every 4 to 6 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy.	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least biannually thereafter.	Physical & Clinical examination Modified Rankin Score Distribution of stiffness score Physical Examination Timed walk	Patient has failed or has contraindications to GABAergic Medications

Indication	Acute 'Rescue' Short Term Use	Long term Maintenance use	Start Criteria	Stop Criteria	Dose	Monitoring	Potential Outcome Measures	Alternative Treatment
Exceptional Use								
Multiple Sclerosis (Relapsing Remitting Multiple Sclerosis RRMS)	Yes	No	Severe relapse unresponsive to high dose steroids or where they are contraindicated. A diagnosis must be made by a neurologist	Course completion	**Initial Dose:** 1-2 g/kg adjusted body weight divided over 2 to 5 days.	Evidence of improvement	Physical & Clinical examination Imaging results EDSS (Expanded Disability Status Scale)	First line: High dose corticosteroids
Paraneoplastic syndrome - Lambert–Eaton myasthenic syndrome (LEMS)	Yes	Yes	IVIG is an option for treatment of LEMS. Objective evidence of clinical improvement is needed for sustained use of IVIG.	If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days. **Maintenance therapy:** 0.4-1g/kg every 4 to 6 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter.	Physical & Clinical examination Imaging results MRC Sum Score	First line: Immunosuppressant
Paraneoplastic syndrome - Paraneoplastic cerebellar degeneration	No	Yes	IVIG treatment should be started within one month of symptom onset and in conjunction with chemotherapy	If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued	**Maintenance therapy:** 2g/kg every 4 to 6 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy	Improvement on objective measures of effectiveness established at the onset of treatment	Clinical examination	Tumour resection and/or oncological treatment are the most effective therapies.
Paraneoplastic syndrome - Paraneoplastic Subacute Sensory Neuropathy	Yes	Yes		If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued	**Maintenance therapy:** 2g/kg every 4 to 6 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy	Improvement on objective measures of effectiveness established at the onset of treatment	Clinical examination	Tumour resection and/or oncological treatment are the most effective therapies.
Encephalopathies - Autoimmune encephalitis mediated by antibodies (NMDAR)	Yes	Repeated courses in exceptional circumstances	Patient must be under neurologist and be treated in conjunction with immunosuppressant's	Course completion	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days.	Improvement on objective measures of effectiveness established at the onset of treatment	Physical & Clinical examination	In conjunction with immunosuppressant or plasmapheresis
Encephalopathies - Autoimmune encephalitis - other (no antibody identified)	Yes	Repeated courses in exceptional circumstances	Recommendation includes but is not limited to potassium channel antibody-associated encephalopathy	Course completion	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days.	Improvement on objective measures of effectiveness established at the onset of treatment	Clinical examination EEG (Neurophysiology)	Alternate treatment options include corticosteroids and Plasma Exchange

Indication	Acute 'Rescue' Short Term Use	Long term Maintenance use	Start Criteria	Stop Criteria	Dose	Monitoring	Potential Outcome Measures	Alternative Treatment
Encephalopathies - Acute disseminated encephalomyelitis (ADEM)	Yes	Repeated courses in exceptional circumstances	IVIG should only be used when ADEM is unresponsive to steroids or they are contraindicated	Course completion	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days.	Improvement on objective measures of effectiveness established at the onset of treatment	Physical & Clinical examination Imaging results	First line: corticosteroids
Encephalopathies - Rasmussen Syndrome/ Rasmussen Encephalitis	Yes	Repeated courses in exceptional circumstances	Diagnosis to be made by neurologist	Course completion	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days.	Improvement on objective measures of effectiveness established at the onset of treatment	Physical & Clinical examination Imaging results MRS score	In conjunction with corticosteroids
Necrotising Autoimmune Myopathy	Yes	Yes	Diagnosis to be made by neurologist or Rheumatologist	If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued	**Initial Dose:** 2 g/kg adjusted body weight divided over 2 to 5 days. **Maintenance therapy:** 0.4-1g/kg every 4 to 6 weeks. Tailor to the lowest dose or longest interval that maintains clinical efficacy	Improvement on objective measures of effectiveness established at the onset of treatment	Physical & Clinical examination Imaging results MRC	First line: corticosteroids Second line: Immunosuppressant

Other indications where IVIG may be indicated:

It is recommended that cases are discussed with MDT or with colleagues prior to initiating treatment with IVIG.

- Immune mediated monofocal neuropathy
- Scaroid Neuropathy
- Immune related cerebellar ataxia
- NORSE (new onset refractory status epilepticus)
- Brachial plexopathy
- Neuromyelitis Optica (NMO)
- MOG associated demyelination
- Sjogren neuropathy
- Antibody negative Autoimmune Epilepsy
- Polymyositis / Dermatomyositis
- Demyelinating neuropathy with anti-MAG antibodies
- PML post-rituximab
- Neuromyotonia
- Peripheral Nerve Hyper excitability disorders

Other indications where IVIG use is not supported:

- Chronic pain

Appendix 1.0 Membership of the IVIG Working Group (February 2022)

- Chair: Dr Orla Hardiman – Consultant Neurologist & National Clinical Programme Lead
  Ms Dervla Kenny – Programme Manager Neurology National Clinical Programme
  Professor Sinead Murphy – Consultant Neurologist
  Dr Christopher McGuigan- Consultant Neurologist
  Professor Aisling Ryan - Consultant Neurologist
  Dr Timothy Counihan- Consultant Neurologist
  Dr Lisa Costelloe - Consultant Neurologist
  Dr Shane Smyth- Consultant Neurologist
  Dr Peter Boers- Consultant Neurologist
  Dr Margaret O'Brien- Consultant Neurologist
  Dr Siobhan Kelly- Consultant Neurologist
  Ms Fionnuala King- Chief Pharmacist, Acute Hospital Drug Management Programme
  Ms Rhona O'Neill- Chief II Pharmacist, Acute Hospital Drug Management Programme

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Appendix 2.0 Revision History

Revision number	Revision date	Summary of changes

References:

1. The Atlantic IVIG Utilization Working Group (2018) *Atlantic Clinical Indications and Criteria for Intravenous and Subcutaneous Immunoglobulin (IVIG/SCIG)* Version 1.0 Halifax, NS
2. Prairie Collaborative Immune Globulin Utilization Management Framework Project. *Criteria for the clinical use of immune globulin*. Alberta Ministry of Health, Shared Health Manitoba, and Saskatchewan Ministry of Health; 2018.
3. Ontario Regional Blood Coordinating Network. *Ontario Immune Globulin (IG) Utilization Management Guidelines* Version 4.0; 2018
4. BC Provincial Blood Coordinating Office IVIG Provincial Program, https: / / www.pbco.ca / index.php / programs / ivig-provincial-program / guidelines-forms-templates July 2019 - adapted for IH IG Utilization Program 25August2020
5. Criteria for the clinical use of immunoglobulin in Australia, Version 3 (the Criteria) https://www.blood.gov.au/bloodstar [Accessed on 11/11/2021]
6. Department of Health. Clinical Guidelines for Immunoglobulin Use. Second Edition Update; July 2011.chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fassets.pu[blishing.service.gov.uk%2Fgovernment%2Fuploads%2Fsystem%2Fuploads%2Fattachment_data%2Ffile%2F216671%2Fdh_131107.pdf&clen=395818&chunk=true](blishing.service.gov.uk%2Fgovernment%2Fuploads%2Fsystem%2Fuploads%2Fattachment_data%2Ffile%2F216671%2Fdh_131107.pdf&clen=395818&chunk=true) [Accessed on 11/11/2021]

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