Evidence-Based Guidelines on the Use of Intravenous Immune Globulin for Hematologic and Neurologic Conditions

Paula Robinson, David Anderson, Melissa Brouwers, Thomas E. Feasby, and Heather Hume, on behalf of the IVIG Hematology and Neurology Expert Panels

In Canada, intravenous immunoglobulin (IVIG) use has increased by 115% over the past 7 to 8 years. Given this increased usage, Canadian Blood Services and the National Advisory Committee on Blood and Blood Products for Canada identified the need to develop and disseminate evidence-based guidelines to facilitate appropriate IVIG use. As a result, guidelines for IVIG use in hematologic and neurologic conditions have been developed and are published in this supplement of Transfusion Medicine Reviews. This commentary provides a brief description of the process used to develop these guidelines and includes a summary of the recommendations for IVIG use in the various conditions evaluated.

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Table 1. Summary of Recommendations for the Use of IVIG in Patients With Hematologic Conditions

<table>
<thead>
<tr>
<th>Hematologic conditions</th>
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<tbody>
<tr>
<td>Acquired hemophilia</td>
</tr>
<tr>
<td>IVIG is not recommended for routine use in the treatment of acquired hemophilia. Based on consensus by the expert panel, IVIG may be considered one option among adjunctive therapies, such as steroids, in urgent situations in this disorder.</td>
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<tr>
<td>Acquired hypogammaglobulinemia (secondary to malignancy)</td>
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<tr>
<td>Adult</td>
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<tr>
<td>Pediatric</td>
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<tr>
<td>Acquired red cell aplasia or pure red cell aplasia (PRCA)</td>
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<tr>
<td>IVIG is not recommended as first line therapy for immunologic PRCA. Based on consensus by the expert panel, IVIG is a reasonable option for patients with immunologic PRCA who have failed other therapies (e.g., prednisone or cyclosporin).</td>
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<tr>
<td>Acquired von Willebrand disease (AvWD)</td>
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<tr>
<td>IVIG is not recommended for routine use in the treatment of AvWD. Based on consensus by the expert panel, IVIG may be considered one option among adjunctive therapies in the treatment of AvWD in urgent situations (e.g., active bleeding or preoperatively).</td>
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<tr>
<td>Aplastic anemia</td>
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<tr>
<td>IVIG is not recommended for the treatment of aplastic anemia.</td>
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<tr>
<td>Autoimmune hemolytic anemia (AIHA)</td>
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<tr>
<td>IVIG is not recommended for routine use in either acute or chronic treatment of AIHA. Based on consensus by the expert panel, IVIG may be considered among the options for treatment of severe life-threatening AIHA.</td>
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<tr>
<td>Autoimmune neutropenia</td>
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<tr>
<td>IVIG is not recommended for routine treatment of autoimmune neutropenia. Based on consensus by the expert panel, IVIG may be considered among the treatment options in rare circumstances of autoimmune neutropenia when the standard of care, G-CSF, fails.</td>
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<tr>
<td>Fetal or neonatal alloimmune thrombocytopenia (F/NAIT)</td>
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<tr>
<td>Treatment of F/NAIT before delivery</td>
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<tr>
<td>Treatment of a newborn with F/NAIT</td>
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<tr>
<td>Hematopoietic stem cell transplantation</td>
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| IVIG is not recommended for use after hematopoietic stem cell transplantation. The panel recognizes as a possible exception to this recommendation that some multinational protocols for (continued on next page)
**Hematopoietic stem cell transplantation** (continued)

the treatment of hematologic malignancies and/or hematopoietic stem cell transplantation in childhood recommend routine use of IVIG for hypogammaglobulinemia. These recommendations are protocol specific and not necessarily consistent across protocols of similar intensity. Consequently, the panel suggests that IVIG may be administered to children registered on such clinical trials to comply with protocol recommendations. However, because the benefit of this approach has not been adequately studied and there is considerable uncertainty as to the efficacy of such an approach, the panel suggests that IVIG not be routinely used for nonregistered patients.

**Hemolytic disease of the newborn (HDN)**

IVIG is not recommended for use in the management of HDN without established hyperbilirubinemia. The panel recommends that IVIG be offered to patients with HDN as treatment for severe hyperbilirubinemia and endorses the recommendations outlined in the American Academy of Pediatrics (AAP) guideline on the management of hyperbilirubinemia. AAP recommendations (July 2004) state: In isoimmune hemolytic disease, administration of IVIG (0.5-1.0 g/kg over 2 h) is recommended if the total serum bilirubin (TSB) is rising despite intensive phototherapy or the TSB level is within 2-3 mg/dL (34-51 μmol/L) of the exchange level. If necessary, this dose can be repeated in 12 h. Although the AAP recommendation states that a dose of IVIG may be given over 2 h, this may represent an infusion administration faster than that recommended by the manufacturer; this needs to be taken into consideration in treatment decisions.

**Hemolytic transfusion reaction**

IVIG is not recommended for either the prophylaxis or routine treatment of hemolytic transfusion reactions. Based on consensus by the expert panel, IVIG may be considered as an option among supportive therapies for urgent situations in this disorder.

**Hemolytic transfusion reaction in sickle cell disease**

IVIG is not recommended for the routine treatment of non-life-threatening delayed hemolytic transfusion reactions in patients with sickle cell disease. Based on consensus by the expert panel, IVIG may be considered among the options for treatment of serious, life-threatening, delayed hemolytic transfusion reactions in patients with sickle cell disease.

**Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP)**

IVIG is not recommended as first-line therapy for HUS or TTP in either the pediatric or adult population. Based on consensus by the expert panel, IVIG may be considered one option among adjunctive therapies when first-line therapy has failed.

**Heparin-induced thrombopathyenia**

IVIG is contraindicated for treatment of heparin-induced thrombopathyenia.

**HIV-associated thrombopathyenia**

IVIG is recommended as a treatment option for HIV-associated thrombopathyenia when there is active bleeding or when platelet counts are less than 10 x 10^9/L.
using the system developed by Bob Phillips et al from the National Health Service (UK) Centre for Evidence-Based Medicine. (A detailed description of the classification system is given in the full guidelines document.)

Using membership lists for appropriate professional organizations, we circulated drafts of the practice guidelines to hematologists and neurologists across Canada, and feedback was obtained via a questionnaire using a web-based survey tool. The results from this consultation process were then reviewed by the expert panels, and subsequent modifications to the guidelines were made where appropriate.

The guidelines produced through this process include a brief clinical description plus a summary of the available evidence and the expert panel’s interpretation and recommendations regarding use of IVIG for each of the conditions reviewed.

HEMATOLOGIC CONDITIONS

For most of the hematologic conditions reviewed by the hematology expert panel, routine use of IVIG was not recommended. Recommendations for routine use of IVIG (i.e., clinical settings in which IVIG could be considered an appropriate therapeutic option) were made for the following

<table>
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<th>Hematologic conditions</th>
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**Table 1** (continued)

**Summary of ASH recommendations:**

- Platelet counts greater than $50 \times 10^9/L$ do not routinely need treatment and should not receive steroids or IVIG. Platelet counts between $30$ and $50 \times 10^9/L$ in first or second trimester also should not receive treatment. Treatment is required if platelet count is $<10 \times 10^9/L$ at any time in the pregnancy or between $10$ and $30 \times 10^9/L$ in second or third trimester or if there is bleeding. Pregnant women who fail steroids and IVIG should be considered for splenectomy in the second trimester if platelet count is less than $10 \times 10^9/L$ and there is bleeding. A platelet count of $50 \times 10^9/L$ is sufficient for vaginal delivery or cesarean section. Intravenous immunoglobulin may be useful if very rapid elevation of platelet count is needed before delivery. These recommendations are based on clinical experience and expert consensus.

**Posttransfusion purpura (PTP)**

- IVIG is recommended as the standard first-line therapy for PTP.

**Viral-associated hemophagocytic syndrome (VAHS)**

- IVIG is not recommended for routine use in the treatment of VAHS.

Based on consensus by the expert panel, IVIG may be considered among the options for treatment of severe life-threatening VAHS.

**Table 2. Summary of Recommendations for the Use of IVIG in Patients With Neurologic Conditions**

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<th>Neurologic conditions</th>
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**Acute disseminated encephalomyelitis (ADEM)**

- IVIG is recommended as an option for treatment of monophasic ADEM when first-line therapy with high-dose corticosteroids fails or when there are contraindications to steroid use.

Based on consensus by the expert panel, IVIG may be considered as an option for treatment of relapsing ADEM to eliminate steroid dependency or for those patients who fail to respond, or have contraindications, to steroids.

**Adrenoleukodystrophy**

- IVIG is not recommended for the treatment of adrenoleukodystrophy.

**Amyotrophic lateral sclerosis**

- IVIG is not recommended for the treatment of amyotrophic lateral sclerosis.

**Autism**

- IVIG is not recommended for the treatment of autism.

**Chronic inflammatory demyelinating polyneuropathy**

- IVIG is recommended as an option for the short-term management of new-onset chronic inflammatory demyelinating polyneuropathy (CIDP) or CIDP relapses.

Based on consensus by the expert panel, IVIG may be considered as an option in combination with other immunosuppressive therapy for the long-term management of CIDP. If IVIG is to be used in the long-term management of CIDP, the patient should be under the care of a qualified expert with specialized knowledge of CIDP, and a systematic approach should be taken to determine the minimal effective dose.

**Critical illness polyneuropathy**

- IVIG is not recommended for the treatment of critical illness polyneuropathy.

**Dermatomyositis**

- Based on consensus by the expert panel, pathologic confirmation by means of a skeletal muscle biopsy is required for the diagnosis of dermatomyositis. It is critical that the muscle specimen be procured, processed, and interpreted in a laboratory familiar with the correct handling of muscle biopsy specimens and that the final interpretation be made by an expert in neuromuscular pathology.

Based on consensus by the expert panel, use of IVIG for the treatment of patients with dermatomyositis should be made in consultation with an expert in neuromuscular disease.

- IVIG is not recommended as monotherapy for dermatomyositis.

- IVIG is recommended as an option, in combination with other agents, for patients with dermatomyositis who have not adequately responded to other immunosuppressive therapies.

- IVIG is recommended, in combination with other agents, as a steroid-sparing option for patients with dermatomyositis.

**Diabetic neuropathy**

- IVIG is not recommended for treatment of diabetic polyneuropathy, mononeuropathy, or proximal lower limb neuropathy.

Based on consensus by the expert panel, IVIG use for patients with diabetes who have evidence of a CIDP phenotype should follow the recommendations outlined in the CIDP section of this guideline.

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Table 2 (continued)

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<th>Neurologic conditions</th>
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**Guillain-Barré syndrome (GBS)**
IVIG is recommended as a treatment option for GBS within 2 wk of symptom onset for
(i) Patients with symptoms of grade 3 severity (able to walk with aid) or greater; or
(ii) Patients with symptoms less than grade 3 severity whose symptoms are progressing.

Based on consensus by the expert panel, IVIG may be considered as a treatment option for patients who initially responded to IVIG and who are experiencing a relapse of symptoms.

Based on consensus by the expert panel, the recommendations for use of IVIG for GBS also apply to patients with Miller-Fisher and other variants of GBS. Diagnosis of GBS variants should be made by a specialist with expertise in this area.

**Inclusion body myositis**
Based on consensus by the expert panel, pathologic confirmation by means of a skeletal muscle biopsy is required for the diagnosis of inclusion body myositis. It is critical that the muscle specimen be procured, processed, and interpreted in a laboratory familiar with the correct handling of muscle biopsy specimens and that the final interpretation be made by an expert in neuromuscular pathology.

IVIG is not recommended for the treatment of inclusion body myositis.

**Intractable childhood epilepsy**
IVIG is not recommended for the treatment of intractable childhood epilepsy.

**Lambert-Eaton myasthenic syndrome**
IVIG is recommended as an option for treatment of Lambert-Eaton myasthenic syndrome. Objective evidence of clinical improvement is needed for sustained use of IVIG.

**Multifocal motor neuropathy**
IVIG is recommended as first-line treatment for multifocal motor neuropathy.

Based on consensus by the expert panel, diagnosis of multifocal motor neuropathy should be made by a neuromuscular specialist because the diagnosis requires very specific electrophysiologic expertise.

**Multiple sclerosis (MS)**
IVIG is recommended as an option for treatment of patients with relapsing-remitting MS who fail, decline, or are not able to take standard immunomodulatory drug therapies. For those patients with rapidly advancing relapsing-remitting MS, consideration should first be given to immunosuppression therapy.

IVIG is not recommended for the treatment of primary or secondary progressive MS.

Based on consensus by the expert panel, IVIG is not recommended for treatment of acute exacerbations of MS, except in patients with severe, refractory, optic neuritis who have had no recovery of vision after 3 months of standard steroid therapy or patients for whom corticosteroid therapy is contraindicated.

Based on consensus by the expert panel, IVIG may be considered as a treatment option for patients with relapsing-remitting MS who are pregnant or breast-feeding or in the immediate postpartum period for women whose exacerbation rate was high before pregnancy and who were on disease-modifying agents before pregnancy with plans to recommence therapy following birth or breast-feeding.

**Myasthenia gravis**

**Adult and juvenile myasthenia gravis**
IVIG is recommended as a treatment option for patients with severe exacerbations of myasthenia gravis or myasthenic crises.

Based on consensus by the expert panel, IVIG may be considered as an option to stabilize patients with myasthenia gravis before surgery.

IVIG is not recommended as maintenance therapy for patients with chronic myasthenia gravis.

**Neonatal myasthenia gravis**
Based on consensus by the expert panel, IVIG may be considered among the treatment options for neonates severely affected with myasthenia gravis.

**Opsoclonus-myoclonus**
Based on consensus by the expert panel, IVIG may be considered as an option for treatment of opsoclonus-myoclonus.

**Paraproteinemic neuropathy (IgM variant)**
IVIG is not recommended for the treatment of IgM paraproteinemic neuropathy.

**Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)**
IVIG is recommended as an option for treatment of patients with PANDAS.

Based on consensus by the expert panel, diagnosis of PANDAS requires expert consultation.

**POEMS syndrome**
IVIG is not recommended for the treatment of POEMS syndrome.

**Polymyositis**
Based on consensus by the expert panel, pathologic confirmation by means of a skeletal muscle biopsy is required for the diagnosis of polymyositis. It is critical that the muscle specimen be procured, processed, and interpreted in a laboratory familiar with the correct handling of muscle biopsy specimens and that the final interpretation be made by an expert in neuromuscular pathology.

Based on consensus by the expert panel, IVIG may be considered among the treatment options for patients with polymyositis who fail to respond to first-line therapies (eg, steroids).

**Rasmussen encephalitis**
IVIG may be an option as a short-term temporizing measure for patients with Rasmussen encephalitis.

IVIG is not recommended for long-term therapy for Rasmussen encephalitis because surgical treatment is the current standard of care.

**Stiff person syndrome**
IVIG is recommended as an option for treatment of stiff person syndrome, if GABAergic medications fail or for patients who have contraindications to GABAergic medications.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.
7 hematologic conditions: acquired red cell aplasia, acquired hypogammaglobulinemia (secondary to malignancy), fetal-neonatal alloimmune thrombocytopenia, hemolytic disease of the newborn, HIV-associated thrombocytopenia, idiopathic thrombocytopenic purpura, posttransfusion purpura.

Intravenous immunoglobulin was not recommended for use, except under certain urgent or life-threatening circumstances, for 8 conditions, namely, acquired hemophilia, acquired von Willebrand disease, autoimmune hemolytic anemia, autoimmune neutropenia, hemolytic transfusion reaction, hemolytic transfusion reaction associated with sickle cell disease, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, and viral-associated hemophagocytic syndrome. Intravenous immunoglobulin was not recommended for aplastic anemia and hematopoietic stem cell transplantation.

Intravenous immunoglobulin was considered to be contraindicated for heparin-induced thrombocytopenia.

Table 1 provides a summary of the recommendations for the clinical use of IVIG for hematologic conditions. For a complete discussion of the panel’s recommendations, including recommended dose and duration of IVIG therapy, please refer to the specific condition of interest in the accompanying guideline article in this issue of *Transfusion Medicine Reviews*.

**NEUROLOGIC CONDITIONS**

Of the 22 neurologic conditions reviewed by the neurology expert panel, specific recommendations for use of IVIG were made for 14 conditions, including acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dermatomyositis, diabetic neuropathy, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis, opsoclonus-myoclonus, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), polymyositis, Rasmussen encephalitis, and stiff person syndrome.

Intravenous immunoglobulin was not recommended for the following 8 neurologic conditions: adrenoleukodystrophy, amyotrophic lateral sclerosis, autism, critical illness polyneuropathy, inclusion body myositis, intractable childhood epilepsy, paraproteinemic neuropathy (IgM variant), and POEMS syndrome.

Table 2 provides a summary of the recommendations for the clinical use of IVIG for neurologic conditions. Please consult the complete guideline for a complete discussion of the panel’s recommendations, including information on recommended dose and duration of IVIG therapy in this issue of *Transfusion Medicine Reviews*.