
DATE: 28 February 2011

CONTEXT AND POLICY ISSUES

Intravenous immunoglobulin (IVIG) is used in the treatment of a wide variety of disorders, to protect the recipient from infection and to suppress immune-mediated or inflammatory disease processes.\(^1\) IVIG is produced from pooled human plasma from several thousand screened volunteer donors, and multiple products are available differing in IgG concentration, additives and stabilizers, and IgA content.\(^1\)

Administration of IVIG requires specific guidelines to ensure patient safety. Similar to administration of other blood products, it is generally recommended that informed consent should be obtained prior to administration.\(^1\) Specific baseline testing should be performed.\(^1\) Requirements for product handling and storage exist because of the nature of the IVIG product.\(^1\) Premedication recommendations may relieve and/or prevent inflammatory symptoms such as headache, chills, fever or nausea,\(^2,3\) and anaphylactoid symptoms, such as hypotension, respiratory distress, chest pain, and shock.\(^1\) Hydration recommendations may reduce thrombotic complications secondary to hyperviscosity, or renal complications.\(^1\) Many infusion-related adverse effects seem related to the rate of administration, and therefore recommendations regarding this rate also become important.\(^1\) Finally, monitoring for development of complications of IVIG therapy should be considered as part of the administration process.\(^1\) Immune globulin may be administered either intravenously, as implied by the name IVIG, subcutaneously or intramuscularly.\(^1\) For subcutaneously administered product, the abbreviation IGSC is the term preferred by regulatory agencies,\(^1\) however some clinical guidelines utilize the term IVIG for all mean pooled normal human immunoglobulin and imply that it can be administered intravenously or subcutaneously.\(^4\)

In 2009, the Ontario Regional Blood Coordinating Network (ORBCoN) published guidelines for clinicians seeking clarification on the common and clinically appropriate uses of Intravenous Immune Globulin (IVIG).\(^2\) They include general recommendations for IVIG Orders, as well as charts that present clinical recommendations by specialty, medical condition, recommendations, and dose and frequency of administration where applicable.

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This report will review the evidence and recommendations and assess the quality of health technology assessments, systematic reviews and meta-analysis and clinical practice guidelines, with a focus on the management and patient safety of IVIG administration in adults or children. This information will be useful in providing evidence based details to inform standard procedures for IVIG administration.

RESEARCH QUESTION

1. What do the clinical practice guidelines recommend on the management and patient safety of IVIG administration?

KEY MESSAGE

Evidence-based recommendations are outlined in select guidelines regarding the management and patient safety of IVIG administration. Limitations related to methodology and applicability are identified.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and January 28, 2011.

Domains identified in the AGREE instrument (Appraisal of Guidelines Research and Evaluation)\(^5\) were used to evaluate the quality of the clinical practice guidelines identified from the literature search, including the *2009 Ontario IVIG Utilization Management Guidelines*.\(^2\) Domains of scope and purpose, stake holder involvement, rigor of development, clarity and presentation, applicability, and editorial independence were assessed.

SUMMARY OF FINDINGS

No relevant health technology assessments, systematic reviews or meta-analysis were identified. Four evidence-based guidelines on the management and patient safety of IVIG administration were identified.\(^2\)\(^4\)\(^6\) Additional articles of potential interest are included in Appendix 1.

Guidelines and recommendations

The Ontario IVIG Utilization Management Guidelines are intended as a guideline document for clinicians seeking clarification on the common and clinically appropriate uses of IVIG and were prepared specifically for use in Ontario.\(^2\) The overall objective of the guidelines is vague and there is not a specific description of scope and purpose. Specific clinical questions covered by the guidelines and the target patient population are not described, though it is implied that the document is intended for all users of IVIG. Recommendations are included for both adult and pediatric indications. The development group is described as the Ontario IVIG Planning Group, which consisted of “medical and technical specialist members from across Ontario”.\(^2\) It is not clear that patients’ views and preferences have been sought. The guidelines were through
review of existing, recently published Canadian guidelines for IVIG utilization, as well as Australian and United Kingdom IVIG utilization guidelines. There is no specified procedure outlined for updating the guidelines. Recommendations are organized by specialty and medical condition in a tabular format. Recommendations pertaining to administration of IVIG are included in a general best practice information section, and it is unclear if they were based on recommendations from other guidelines or strictly expert consensus. An IVIG Utilization Management Toolkit of examples of procedures and forms that relate to recommended practices is available to accompany these guidelines. Potential organizational barriers in applying the guidelines are mentioned as recommendations, but not discussed in detail. There is no discussion on the cost implications or key review criteria for monitoring and/or audit purposes. Details regarding editorial independence are not evident. These guidelines offer limited recommendations regarding the management of IVIG administration. They provide general guidance regarding information that should be included in a utilization guideline or standard operating procedure.

The Use of Immunoglobulin Therapy for Patients with Primary Immune Deficiency: An Evidence-Based Practice Guideline clearly outlined their scope and purpose and are intended for adult and pediatric patients with primary immune deficiency. Clinical questions covered by the guideline were identified by a panel of Canadian physician experts from large pediatric and adult tertiary care centers responsible for the care of patients with primary immune deficiency, using a modified Delphi process. Clinical questions relevant to the administration of IVIG included; “Does treatment with immunoglobulins decrease the frequency of infection, hospitalization, end-organ damage, or malignancy; ameliorate coexistent autoimmune disease; and/or improve survival and quality of life?” “Are there differences in efficacy according to the route of administration of immunoglobulins, that is, intravenous compared to subcutaneous administration?“ “Are there differences in efficacy according to the manufacturer of IVIG?” “Is there a target IgG trough level that should be used to guide treatment decisions in the absence of hard outcomes, for example, mortality, infections?” and “What are the adverse effects of immunoglobulin treatment in patients with primary immune deficiency?” Stakeholder involvement in guideline development was appropriate. National and international experts and patient representatives reviewed the final guideline to validate the relevance of the guideline and each recommendation. Evidence used to support the development of the guidelines was obtained through a systematic review of the literature which included randomized controlled trials, cohort studies, case series, systematic reviews or guidelines. The levels of evidence and grades used for each recommendation were adapted from the Canadian Task Force on Preventative Health Care, and are outlined in Appendix 2. The levels of evidence describe the methodological rigor of the study, whereas the grades of recommendation comprise the level of evidence and clinical expertise. Areas of disagreement were resolved through consensus. It is specified that The National Advisory Committee on Blood and Blood Products will ensure adequate dissemination of the guideline, will assess its utilization and perform periodic revisions to ensure that recommendations reflect current practice and expertise. Recommendations are clearly presented but do not appear to be supported with tools for application. A discussion of potential organizational barriers in applying the recommendations is included, though the potential cost implications of applying the recommendations are not discussed. The guideline proposes that a national registry be established to track patient characteristics in outcomes and a surveillance system for adverse reactions to IVIG. Editorial independence is appropriate as the funding body did not have any role in the selection of panel members, the literature search, the selection of articles, or the development of recommendations. Conflicts of interest of guideline development members are recorded. This guideline provides select evidence based recommendations for administration of IVIG which address questions relating to patient safety,
though they were not focused on administration processes. They are intended for use in patients with primary immune deficiency.

The Royal College of Nursing Standards for Infusion Therapy describe specific standards and guidance for the administration of IVIG. They are intended to help practitioners ensure that patients receive the most appropriate care for their individual circumstances. There is not a clear description of the scope and purpose. It is implied that the target population includes all patients receiving IVIG. The standards were developed by Nurse Specialists, Consultants and Nurse Practitioners. The description of target users is vague, and briefly outlined for the standards and guidance sections. The development of the standards did include an extensive external peer review, including multi-professional organizations. Systematic methods used for searching and selecting evidence were not described, nor were methods used for formulating the recommendations.

Both standards and guidance sections include references to relevant supporting literature and further reading. Each reference is graded as follows:

I. Randomized controlled trials, including meta-analysis
II. Non-randomized controlled trials and retrospective studies
III. Clinical experience and anecdote, includes guidelines based on expert opinion and multiple sources of evidence which may include randomized studies.

A clear procedure for updating the standards is not provided. The recommendations are specific and easily identified. They are not supported with tools for application. Standards that discuss potential organizational barriers are included but those that consider potential cost implications of applying the recommendations are not. Criteria for evaluating compliance are provided in the guidance section. Details pertaining to editorial independence are not discussed. These standards provide detailed and practical recommendations and guidance on the administration of IVIG. The recommendations are referenced, but their quality, however, remains unclear.

Clinical Guidelines for Immunoglobulin Use were developed by the Department of Health in the United Kingdom. There are clearly defined aims prospectively developed by the Guideline Development Group. The clinical questions covered by the guidelines are not specifically described. Guideline development included multidisciplinary participation. Patient organizations were consulted in the creation of the guidelines. The target audience is not outlined within the guideline, but is included in the accompanying Department of Health Information Reader Box, as “PCT CEs, NHS Trust CEs, SHA CEs, Foundation Trust CEs, Medical Directors, Directors of Finance, general practitioners, communication leads, emergency care leads, and chief pharmacists”. There is no legend of abbreviations included for this description, and it is not explicit that the guidelines were piloted among target users. A systematic review of the literature was conducted to identify evidence-based IVIG guidelines; however the approach was not as rigorous as undertaking an independent systematic review of all available evidence. The methods used for formulating the recommendations are clearly defined, and it is clear that the guidelines were externally reviewed by experts. There is an explicit link between the recommendations and the supporting evidence for most recommendations. These recommendations for specific indications were assessed and graded according to the strength of supporting evidence based on the US Department of Health and Human Services Agency for Healthcare Policy and Research (AHPCR) system. Of note, the recommendations relating to administration were not graded. There is a clear procedure
described for updating the guidelines. Recommendations are specific and different options for management of the condition are clearly presented. Key recommendations are easily identifiable. The guidelines are supported with a patient leaflet. Select organizational barriers in applying the recommendations are discussed, including that all patients must undergo an annual efficacy review in line with Good Clinical Practice. Outcomes of these annual reviews must be entered into a National Immunoglobulin Database, presenting criteria for monitoring and/or audit. Cost implications are considered. Details pertaining to editorial independence are not discussed. These guidelines do not provide significant contributions with respect to evidence based recommendations focused on management of administration.

A summary of recommendations from these four relevant guidelines with a focus on management and patient safety of IVIG administration in adults or children are reported in Table 1.

Table 1. Recommendations for Management and Patient Safety of IVIG Administration

<table>
<thead>
<tr>
<th>Title, Group, Year of Guidelines Publication</th>
<th>Recommendations Identified in the Guideline</th>
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<tbody>
<tr>
<td>Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines, ORBCoN, 2009</td>
<td>▪ Best practices for infusion of IVIG should be available at each institution using IVIG.²</td>
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<td>▪ New orders for IVIG should be checked prospectively at the site where the order is made, preferably through an SOP applied through the blood transfusion service or pharmacy, where the IVIG orders are received and product is dispensed.²</td>
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<td>▪ Conduct and document regular monitoring of patient’s weight for patients who use IVIG over a period of time.²</td>
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<td></td>
<td>▪ Monitor platelet counts in ITP patients using IVIG.²</td>
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<td></td>
<td>▪ Conduct regular testing of patients to detect hemolysis arising from the use of IVIG.²</td>
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<td></td>
<td>▪ Clear direction on the practice of rounding up and rounding down of IVIG doses.²</td>
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<td></td>
<td>▪ Hospitals should monitor, collect and report specific information on wastage of IVIG to ORBCoN.²</td>
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<td></td>
<td>▪ Perform and document pre infusion serum immunoglobulin levels for Primary and Secondary Immune Deficiency patients (baseline and trough).²</td>
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<tr>
<th>The Use of Immunoglobulin Therapy for Patients with Primary Immune Deficiency: An Evidence-Based Practice Guideline,</th>
<th>Recommendations (Level of evidence, grade of recommendation)</th>
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<tr>
<td></td>
<td>▪ An immunologist should be consulted for all pediatric and adult patients with primary immunodeficiency syndromes with deficient antibody responses before the administration of immunoglobulin.³ (III, B)</td>
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<td>▪ Before treatment with immunoglobulins, laboratory assessment of patients should include assessment of all immunoglobulin isotypes (IgG, IgA, IgM, IgE) and (2) in vivo response to protein and polysaccharide vaccines. Additional laboratory assessment includes (1) a complete blood count and lymphocyte count, (2) B-and T- cell enumeration (3) assessment of end-organ damage, (4) genetic diagnosis if possible, and may include (5) T- and B-cell proliferation studies.³ (III, B)</td>
</tr>
<tr>
<td>Title, Group, Year of Publication</td>
<td>Recommendations Identified in the Guideline</td>
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| **Canadian Blood Services and National Advisory Committee on Blood and Blood Products, 2010**<sup>3</sup> | - With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one manufacturer of IG over another for currently available products.<sup>3</sup> (I to II-2, I)  
- With respect to clinical efficacy for reducing infections, IVIG and SCIG preparations should be considered equivalent.<sup>3</sup> (I and II, B)  
- When deciding on route of administration, patient preference should be taken into account.<sup>3</sup> (III, A)  
- Do not give intramuscular immunoglobulin for replacement therapy for primary immune deficiency.<sup>3</sup> (I, D)  
- To minimize rate-related reactions, follow product specifications.<sup>3</sup> (III,B)  
- Aim to achieve a minimum IgG trough level of 7g/L in most patients.<sup>3</sup> (III,B)  
- Monitor IgG trough levels every 3 to 6 months in growing patients and every 6 to 12 months in adult patients.<sup>3</sup> (III, B)  
- Because immunoglobulin is a human-derived blood product, with a possibility of home administration, it is recommended that the agency that dispenses the IG product ensures ongoing traceability of the donor source of immunoglobulin and that the prescribing practitioner ensures a record of distribution and administration is kept.<sup>3</sup> (III,A)  
- Report adverse events to the transfusion service supplying the immunoglobulin product.<sup>3</sup> (III,A) |
| **Royal College of Nursing Standards for Infusion Therapy, Royal College of Nursing, 2010**<sup>6</sup> | **Standard (Levels of evidence: III)**  
- IVIG should be prepared and administered using aseptic technique and sterile or non sterile gloves. Aseptic technique with sterile gloves may be used for administration of intravenous medications via a central venous access device  
- The nurse administering IVIG should be knowledgeable about the indications for IVIG therapy, normal dosage, side effects, precautions and contraindications, potential adverse reactions and the appropriate interventions  
- Measures should be taken to minimize the risk of allergic/anaphylactic reactions during the administration of IVIG  
- IVIG should be administered in a safe, appropriate environment (p.55)<sup>6</sup> |
|  | **Guidance (Levels of evidence: III)**  
- Protocols for administration of IVIG should be set out in organization policies and procedures  
- Prior to commencing IVIG, informed, written consent must be obtained from the patient or person with parental responsibility if the patient is a child. This should include the risk of infection, the process of infusion and adverse reactions that may occur. The consent process should be documented in the medical record  
- The patient must have an infusion partner/carer who agrees to be trained to administer the IVIG infusion  
- IVIG should be prepared, stored, and administered according to the |
manufacturer’s guidelines. Once prepared the infusion should be labeled. Once the IVIG has been reconstituted it should be administered promptly as it contains no preservatives (check manufacturer’s instructions)

- The IVIG infusion should be started slowly and the rate increased in incremental steps until the patient’s maximum infusion rate is reached. Once tolerance has been established, the infusion can be administered more rapidly. This procedure should be followed each time the brand of IVIG is changed. Side effects and adverse reactions are reduced by avoidance of rapid infusion rates.
- Infusion rates are calculated at mL/kg/minute. It is important that an accurate weight is used to calculate the infusion rate.
- The administration set used to administer IVIG may require a 15-micron filter to prevent infusion of undissolved immunoglobulin or other foreign material into the patient. Check manufacturer’s instructions as not all products require a filter.
- The patient should be observed during infusion of IVIG for signs of an adverse reaction. Baseline observations of pulse, blood pressure and temperature should be recorded. These should only be repeated as indicated. Observations every 5-15 minutes will be necessary if the patient experiences a reaction.
- Common side-effects such as headache and slight hypotension may be alleviated by slowing the infusion rate.
- Flu-like symptoms can be treated with the administration of either paracetamol or ibuprofen pre- and post-infusion.
- Post-infusion headaches accompanied by nausea and vomiting (aseptic meningitis) can occur from 12 hours to several days after the IVIG. This may be treated by administration of antihistamines, corticosteroids and hydration before the infusion and analgesia post-infusion as necessary. These symptoms may be relieved by administering IVIG as a 24-hour infusion. Using an alternative IVIG product may prevent recurrence of the headache.
- Anaphylaxis/allergic reactions are rare and are associated with the first infusion of IVIG or when products are changed. If a reaction occurs, antihistamines, corticosteroids, and adrenaline may be required. An emergency trolley and oxygen should be readily available during first infusion or brand change of IVIG. This type of reaction diminishes with subsequent infusions. Pre-medication with antihistamine and corticosteroid lessens the risk of a reaction.
- If an adverse event occurs the necessary action should be instigated, the event should be reported to the prescriber/patient’s consultant and documented in the patient record.
- First and second doses of IVIG should be administered in a hospital setting. Where the brand is changed, the first and second doses of the new brand should also be administered in a hospital setting.
- If a patient has an active infection present the IVIG should be delayed for a
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<th>Recommendations Identified in the Guideline</th>
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<td>few days until the infection has been treated with antibiotics. An adverse reaction is more likely to occur if an infection is present.</td>
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<td>▪ Methods should be employed to minimize the risk of pathogen transmission via IVIG.</td>
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<td>▪ If the patient is deficient in immunoglobulin A (IgA) and has high titre anti-IgA antibodies the patient should receive IgA-depleted immunoglobulin.</td>
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<td>▪ The batch number should be recorded to facilitate rapid identification of contaminated batches.</td>
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<td>(pp.55-57) 6</td>
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<td><strong>Home Administration</strong></td>
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<td>▪ If IVIG is administered in the home setting by a community nurse, patient, parent or caregiver, the person administering the IVIG should be able to recognize the side effects and signs of an allergic/anaphylactic reaction and take the appropriate actions. A pre-filled syringe containing adrenaline should be readily available for use and the caregiver taught to seek medical help/call an ambulance should an allergic/anaphylactic reaction occur.</td>
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<td>▪ If IVIG is to be administered in the home setting the caregiver/patient/parent should be educated in the preparation and administration of IVIG, hand-washing, aseptic technique, use of any delivery system, venipuncture, blood sampling, correct infusion rates, disposal of used equipment, immediate and long-term side effects, potential adverse reactions, and instructed in the use of pre-filled adrenaline syringes.</td>
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<td>▪ Patients and carers trained to administer IVIG in the home should be formally trained by a specialist immunology nurse. The specialist nurse must be competent in the administration of intravenous medication, possess a teaching and assessing certificate or equivalent, and have experience of home intravenous therapy training.</td>
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<td>▪ The agreement of the GP and/or primary care trust should be obtained and mechanisms for funding established before instigating a home training program. In addition, a system for prescribing the IVIG should be in place and arrangements made for the supply of the IVIG/other equipment by a community pharmacy service or hospital pharmacy</td>
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<td>▪ Before starting home administration of IVIG the patient should have experienced no adverse reactions/events for 4-6 months</td>
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<td>▪ Patients receiving IVIG in the home setting must have telephone access, in order to call the emergency services</td>
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<td>▪ Patients receiving IVIG in the home setting must agree to continue monitoring and review as determined by the specialist hospital. Monitoring includes blood samples for liver function, trough IgG levels and CRP. Additional samples may be required at least yearly for functional antibodies, full blood count with haematinsics as required, anti-IgA antibodies, hepatitis BsAg and hepatitis C PCR and store serum.</td>
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<td>▪ The competence of the patient/infusion partner should be assessed yearly</td>
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<td>▪ The use of permanent venous access devices should be avoided where possible as the patient has an increased susceptibility to infection, however</td>
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when necessary the patient receiving long-term IVIG therapy should be considered for placement of an appropriate venous access device. (pp.55-56)

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<td>Pharmacists and prescribers are recommended to “round down” the dose to the nearest whole vial in an effort to conserve drug volumes.</td>
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<tr>
<td>Pharmacists and prescribers will continue the policy of brand consistency for patients on long-term IVIG.</td>
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<tr>
<td>Subcutaneous immunoglobulin is therapeutically equivalent to IV therapy and may be considered first line. It can be given if the patient has poor veins, adverse reactions to IV products or for patient preference.</td>
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Long term users

Primary Immunodeficiencies

CRP: C-reactive protein; GP: general practitioner; hepatitis BsAg: hepatitis B surface antigen; IG: immunoglobulin; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IVIG: intravenous immunoglobulin; ITP: idiopathic thrombocytopenic purpura; ORBCoN: Ontario Regional Blood Co-ordinating Network; paracetamol: acetaminophen; PCR: polymerase chain reaction; SCIG: subcutaneous immunoglobulin; SOP: standard operating procedure

Limitations

In addition to the 2009 Ontario IVIG Utilization Management Guidelines, three other relevant evidence based guidelines were identified that included recommendations on the management and patient safety of IVIG administration. The Ontario guidelines were not prepared in a rigorous manner according to the AGREE Instrument, and recommendations specifically pertaining to the administration of IVIG are not explicitly linked to supporting evidence. The recommendations related to administration are vague and arbitrary. The Canadian guideline, which the Ontario guidelines reference, includes a systematic review and was developed using a rigorous methodology. It offers only selected recommendations specific to the process of administration of IVIG as it was not the focus, however some of their prospectively determined clinical questions were relevant. This guideline is intended to apply to patients with primary immune deficiency, which potentially limits their applicability to other populations. Other Canadian evidence based practice guidelines for IVIG use that focused on other indications do not include recommendations related to administration. The Royal College of Nursing Standards for Infusion Therapy includes detailed, practical standards and extensive guidance specific to the administration of IVIG. It is not clear that these guidelines are developed using a rigorous methodology; they do not include a systematic review or describe methods of development. They do include references to supporting literature with explicit links between the recommendations and the supporting evidence, however all of the supporting literature for the administration of IVIG is graded at the lowest level (III), indicating it is clinical experience and anecdote, includes guidelines based on expert opinion and multiple sources of evidence which may include randomized studies. Clinical Guidelines for Immunoglobulin Use, also from the United Kingdom, offer select recommendations related to administration, though they are more closely related to dispensing practices and route of administration. These guidelines include a systematic review of other evidence based guidelines, limiting the rigour of the methodology. There is an explicit link between most of the recommendations and
supporting evidence, and most are graded. The few recommendations related to the management of administration, however, are not explicitly referenced or graded. Another limitation for the two documents from the United Kingdom\textsuperscript{4,6} is the possibility of limited generalizability of specific recommendations, standards, or guidance to the Canadian health care setting. A specific example is the detailed guidance relating to home administration of IVIG; in Canada, self-infusing of IVIG at home is currently only available in Quebec.\textsuperscript{3}

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

Evidence-based recommendations developed using rigorous methodology for management and safety of IVIG administration are provided in the Canadian guideline\textsuperscript{3} for use in patients with primary immune deficiency. They include recommendations for consultation with an immunologist prior to administration of immunoglobulin, specific laboratory assessment prior to treatment, choice of route of administration, minimization of infusion rate-related reactions through consultation of product specifications, trough level monitoring, traceability of donor source, recording of distribution and administration and reporting of adverse events. Although limitations were identified in the rigour of development, the Royal College of Nursing Infusion Standards\textsuperscript{6} are clearly referenced, and provide more detailed standards and guidance for nurses focused on the administration of IVIG including its preparation, infusion, pre-medication, administration settings and monitoring and management of adverse reactions. The Ontario guidelines\textsuperscript{2} provide only general guidance for information related to administration of IVIG. Clinical Guidelines for Immunoglobulin Use\textsuperscript{4} do not offer directly referenced recommendations focused on management of administration.

The Canadian guideline\textsuperscript{3} and the Royal College of Nursing Infusion Standards\textsuperscript{6} provide some evidence to inform the development of a procedure for the administration of intravenous immunoglobulin. There exists a gap in the available literature with respect to information on management and patient safety of administration of IVIG in patient populations other than those with primary immune deficiency. A need for high level evidence supporting many of the processes recommended for administration of IVIG still exists.

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**REFERENCES:**


APPENDIX 1. References identified for additional information
Guidelines (not evidence-based)


Standard Operating Procedures


Other


APPENDIX 2. Canadian Task Force on Preventative Health Care Grades of Recommendations and Levels of Evidence

Recommendation Grades for Specific Clinical Preventive Actions
A The CTF concludes that there is **good** evidence to recommend the clinical preventive action.

B The CTF concludes that there is **fair** evidence to recommend the clinical preventive action.

C The CTF concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making.

D The CTF concludes that there is **fair** evidence to recommend against the clinical preventive action.

E The CTF concludes that there is **good** evidence to recommend against the clinical preventive action.

I The CTF concludes that there is **insufficient** evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

The CTF recognizes that in many cases patient specific factors need to be considered and discussed, such as the value the patient places on the clinical preventive action; its possible positive and negative outcomes; and the context and/or personal circumstances of the patient (medical and other). In certain circumstances where the evidence is complex, conflicting or insufficient, a more detailed discussion may be required.

**Levels of Evidence - Research Design Rating**

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<tr>
<td>I</td>
<td>Evidence from randomized controlled trial(s)</td>
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<tr>
<td>II-1</td>
<td>Evidence from controlled trial(s) without randomization</td>
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<tr>
<td>II-2</td>
<td>Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group</td>
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<tr>
<td>II-3</td>
<td>Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here</td>
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<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees</td>
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