Polyclonal Intravenous Immunoglobulin in Patients with Immune Thrombocytopenic Purpura: Clinical Systematic Review
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Polyclonal Intravenous Immunoglobulin in Patients with Immune Thrombocytopenic Purpura: Clinical Systematic Review

Stella Chen, MD MSc
David Pi, MBBS FRCPC
Mohammed Ansari, MBBS, MMedSc, MPhil
Lorri Puil, MD, PhD
Brigitte Desjardins, BSc MSc
Raymond Banks, AB MA MLS

March 2008

1 Canadian Agency for Drugs and Technology in Health, Ottawa ON
2 British Columbia Ministry of Health, Vancouver BC
3 Chalmers Research Group, Ottawa ON
4 At the time of report development, Dr. Lorri Puil was affiliated with the Chalmers Research Group, Ottawa ON
5 RTI Health Solutions, Ottawa ON
Reviewers

These individuals kindly provided comments on this report.

External Reviewers

Man-Chiu Poon, MD MSc
Professor of Medicine
Pediatrics and Oncology
University of Calgary
Calgary, AB

Tanya Horsley, PhD
Investigator
Epidemiology and Community Medicine
University of Ottawa
Ottawa, ON

CADTH Peer Review Group Reviewers

Rick Audas, BBA MBA MA (Economics) PhD
Assistant Professor
Faculty of Medicine
Memorial University of Newfoundland
St. John’s, NL

Dean Fergusson, MHA PhD
Senior Scientist
Ottawa Health Research Institute
Ottawa, ON

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Authorship

Stella Chen was responsible for addressing external reviewers’ comments and updating the drafts, incorporating data from new studies identified through the updated literature search, and the drafting of the executive summary.

David Pi was responsible for providing clinical expertise and advice to the project team and for critical review of the interim and final drafts of the report.

Mohammed Ansari completed the design, data extraction, data synthesis, and interpretation of data and drafted the report, including the results and discussion.

Lorri Puil led the protocol development, provided clinical content and methodological expertise, supervised the literature review, selected studies, analyzed and interpreted data, drafted the report, and reviewed the final draft.

Brigitte Desjardins was responsible for revisions and rewriting of the report, including the reorganization of data and tables.
Raymond Banks was responsible for updating the literature search and for authenticating and formatting the bibliographies.

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Conflicts of Interest
No conflicts of interest have been declared.
Polyclonal Intravenous Immunoglobulin in Patients with Immune Thrombocytopenic Purpura: Clinical Systematic Review

Technology
Polyclonal intravenous immunoglobulin (IVIg).

Conditions
Acute and chronic idiopathic thrombocytopenic purpura (ITP) in children and ITP in adults.

Issue
IVIg is highly utilized, especially in ITP. The potential availability of less costly alternative treatments for these conditions and the uncertainty of a therapeutic advantage of IVIg over alternate therapies suggest an assessment to inform decisions is necessary.

Methods and Results
Twenty-eight randomized controlled trials were identified that compared IVIg with corticosteroids, anti-D immunoglobulin, or close observation in adults and children with ITP. Most trials were of poor quality. Many trials were of limited quality.

Implications for Decision Making
• Evidence suggests IVIg can improve health in children with acute ITP. IVIg (0.8 to 1 g/kg/day over one to two days) is more efficacious than corticosteroids in terms of early improvement of thrombocytopenia to platelet counts greater than or equal to 20x10^9/L. The relative efficacy of IVIg in comparison with high doses of methylprednisolone of 30 mg/kg remains inconclusive.
• Compelling evidence is lacking for other indications. The role of IVIg in chronic childhood ITP could not be established. IVIg also does not have a clear advantage over other interventions for the long-term management of adult ITP.
• No evidence is available to inform some decisions. There is no relevant information available to identify subgroups of ITP patients who may preferentially benefit from IVIg.

This summary is based on a comprehensive health technology assessment available from CADTH’s web site (www.cadth.ca): Chen S, Pi D, Ansari M, Puil L, Desjardins B, Banks R. Polyclonal Intravenous Immunoglobulin in Patients with Immune Thrombocytopenic Purpura: Clinical Systematic Review.
EXECUTIVE SUMMARY

The Issue
Canada has one of the highest per capita rates of consumption of intravenous immunoglobulin (IVIg) in the world. The rate has been increasing annually over the past decade. The escalating cost, increasing demand for an expanding number of indications, and a recent IVIg shortage has prompted Canadians to adopt new approaches to manage its use. Assessing the impact of IVIg use in patients with immune (idiopathic) thrombocytopenic purpura (ITP) (an approved indication) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (an off-label indication) has been identified as a priority, given the high utilization rates for these indications in Canada. The highest use of IVIg occurs in the pediatric population with ITP. The potential availability of less costly alternative treatments for these conditions and the uncertainty about a therapeutic advantage of IVIg over alternative therapies are additional reasons for prioritizing this assessment in Canada. The focus of this report is on ITP. CIDP will be addressed in a future assessment.

Objectives
The objectives of the project were to determine the role of IVIg in the treatment of ITP by addressing the following research questions:

- Does IVIg have an incremental benefit in treating ITP over alternative standard therapy?
- What place does IVIg have in the management of acute or chronic ITP in children or adults?
- Is there sufficient evidence to identify subgroups of ITP patients who may preferentially benefit from IVIg?

Methods
Literature was obtained by searching multiple databases and by contacting manufacturers. Included were all full reports of published randomized controlled trials that enrolled patients with ITP. The selection of studies, data extraction, and study quality assessment were performed by two reviewers independently or by one reviewer and subsequently verified by another reviewer.

Outcomes for this review were reduction in bleeding (for acute ITP in children), deferred splenectomy (for chronic ITP in children and ITP in adults), and time to a platelet count of greater than or equal to 20x10^9/L or greater than or equal to 50x10^9/L (all ITP categories).

Results
Twenty-eight randomized controlled trials were included in this review. IVIg was compared with corticosteroids, anti-D immunoglobulin, modified or different doses of IVIg, or close observation. Most of the included studies were of low quality.

Acute ITP in Childhood: When IVIg was compared with corticosteroids, five of 11 relevant trials suggested that IVIg showed superior efficacy in the early recovery of profound thrombocytopenia. Six trials failed to show a significant result in favour of IVIg or corticosteroid. Quantitative data syntheses indicated that children with acute ITP who had platelet counts less than 20x10^9/L were 55%, 34%, and 17% more likely to achieve counts greater than or equal to 20x10^9/L, at 24 hours, 48 hours, and 72 hours after the start of treatment with IVIg compared with corticosteroids. When IVIg was compared with anti-D immunoglobulin in two trials, the quantitative synthesis of the scant evidence was indeterminate for the outcome, the proportion of patients who achieved a platelet count greater than 20x10^9/L at 24 hours [relative risk (RR) 1.52, 95% CI 0.92 to 2.52]. A reduction in...
hemoglobin with anti-D immunoglobulin was reported in both trials, but the difference between the two groups was not statistically significant in one trial, and the statistical significance was not reported in the other. In one trial that compared IVIg with close observation, IVIg was associated with earlier improvements in platelet counts.

**Chronic ITP in Childhood:** When IVIg was compared with corticosteroids, one study reported that IVIg was superior for a short-term platelet response, whereas corticosteroids was more favourable for a long-term improvement in platelet counts. Another study concluded that IVIg was not significantly better than corticosteroids in improving platelet counts, reducing severe bleeding episodes and days of severe bleeding, and deferring splenectomy. When compared with anti-D immunoglobulin, the proportion of patients with deferred splenectomy was similar in both groups in one trial.

**ITP in adults:** Two trials compared IVIg with corticosteroids in adults with newly diagnosed ITP. One study found no advantage for IVIg compared with oral prednisone in the improvement of platelet counts, time to peak platelet count, and deferral of splenectomy. In the other study, IVIg was superior to intravenous methylprednisolone in the short-term improvement of thrombocytopenia. IVIg was associated with more severe adverse events that prolonged hospitalization.

**Conclusions**
This review examined the clinical effectiveness of using IVIg in the management of patients with ITP, compared with other active treatments or placebo.

For acute ITP in children, inconsistent results were reported across studies regarding IVIg superiority in the early recovery of profound thrombocytopenia. Our quantitative synthesis shows significant differences in the proportion of patients with platelet counts greater than or equal to $20 \times 10^9/L$ at 24 hours, 48 hours, and 72 hours after the start of treatment, in favour of IVIg compared with corticosteroids. In adult patients with profound thrombocytopenia, the effect of IVIg on clinical outcomes remains indeterminate. Sparse evidence indicates that IVIg may be more efficacious in improving platelet counts in the short term than corticosteroids but possibly at the risk of more SAEs.

Until further adequately powered and controlled trials are available, the clinical impact of choosing these agents versus available alternatives in most situations remains uncertain. For acute ITP in children, our findings showed that IVIg (0.8 g/kg/day to 1 g/kg/day over one to two days) is more efficacious than corticosteroids in terms of the early improvement of thrombocytopenia to platelet counts greater than or equal to $20 \times 10^9/L$. The role of IVIg in chronic childhood ITP could not be established because evidence from scant, poorly designed, and poorly reported randomized controlled trials could not be synthesized. There are insufficient data to determine whether IVIg has an advantage over other interventions in the long-term management of adult ITP. Finally, there is insufficient evidence to identify subgroups of ITP patients who may preferentially benefit from IVIg.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>CI</td>
<td>confidence intervals</td>
</tr>
<tr>
<td>CIDP</td>
<td>chronic inflammatory demyelinating polyradiculoneuropathy</td>
</tr>
<tr>
<td>F(ab)</td>
<td>fragment antigen binding</td>
</tr>
<tr>
<td>Fc</td>
<td>fragment crystallizable</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HTA</td>
<td>health technology assessment</td>
</tr>
<tr>
<td>ICH</td>
<td>intracranial hemorrhage</td>
</tr>
<tr>
<td>ITP</td>
<td>immune (idiopathic) thrombocytopenic purpura</td>
</tr>
<tr>
<td>IVIg</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>Rh−</td>
<td>rhesus negative</td>
</tr>
<tr>
<td>Rh+</td>
<td>rhesus positive</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>TAE</td>
<td>total adverse event</td>
</tr>
<tr>
<td>WDAE</td>
<td>withdrawals due to adverse event</td>
</tr>
</tbody>
</table>
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1 INTRODUCTION

1.1 Background

In Canada, intravenous immunoglobulin (IVIg) use is approved for six indications: primary immunodeficiency, hypogammaglobulinemia, immune or idiopathic thrombocytopenia purpura (ITP), pediatric human immunodeficiency virus (HIV), bone marrow transplantation, and B-cell chronic lymphocytic leukemia.1 IVIg, however, is used for many off-label indications, and off-label use is expanding.

Ninety indications were identified (with 17% to 29% of use unknown) in a retrospective audit of IVIg use at 10 teaching and community hospitals (two pediatric and eight adult centres) in Ontario, Quebec, Alberta, and British Columbia from 1997 to 1999.2 ITP accounted for the highest total use of IVIg in the adult and pediatric populations.

In a study on IVIg prescribing practices between 1995 and 2000 in four Toronto hospitals (representing most of the adult medical and surgical specialists except obstetrics and gynecology), ITP was the most common hematological indication and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) the most common neurological indication.3 More recently, CIDP and ITP were reported as leading indications for total IVIg use in the four Atlantic provinces.4

1.1.1 Idiopathic thrombocytopenic purpura

ITP results from an abnormal immune response to disease-related or indeterminate antigens, with accelerated immune-mediated destruction of platelets by the reticuloendothelial system, especially the spleen. Heterogeneity may exist in terms of the alteration in the immune response.5 The estimated annual incidence of immune thrombocytopenia is 100 cases per million people, with approximately 50% of cases in children.6 Because the natural history of ITP differs in children and adults, this report considers the two groups separately.

1.1.2 Acute ITP in Children

Acute ITP in children is a diagnosis of exclusion, tends to have an abrupt onset, and often follows a viral illness or immunization (for example, measles, mumps, and rubella vaccine). The disease is characterized by a low platelet count (less than 150×10⁹/L) and mucocutaneous bleeding (petechiae, purpura). Estimates of the incidence of childhood acute ITP are 4.0 to 5.3 per 100,000, and of chronic ITP are 0.46 per 100,000, with a prevalence of 4.6 per 100,000.7 Children usually present with a short history of purpura over 24 to 28 hours and have a platelet count less than 10×10⁹/L to 20×10⁹/L. The disorder resolves spontaneously, in most cases within six months, and may be characterized by single or multiple episodes. The most serious complication is life-threatening intracranial hemorrhage (ICH), which is estimated to occur in 0.1% to 1% of children with acute ITP.8

The goal of treatment is to prevent serious and potentially fatal bleeding with minimal treatment-related adverse events (AEs). Treatment has generally been based on the platelet count as a surrogate marker for bleeding risk. A platelet count of less than 20×10⁹/L, if accompanied by mucosal bleeding (“wet purpura”) or a platelet count of less than 10×10⁹/L without evidence of bleeding, is often the threshold used.
In a prospective international survey using the Childhood ITP Registry, current management approaches were heterogeneous, as were the approaches used by surveyed pediatric hematology-oncology specialists in the US. Options include close observation but no treatment, IVIg, anti-D immune globulin [in rhesus positive (Rh+) non-splenectomized children], corticosteroids, a combination of immune globulin and steroids, plasma exchange, and in rare cases, splenectomy. Children who have life-threatening bleeding are treated with multiple modalities, including IVIg, intravenous methylprednisolone, and platelet transfusions. In a retrospective study, a minority of children who had a major bleeding episode had a rise in platelet count within 24 hours after receiving intravenous treatment with IVIg, corticosteroids, or both.

1.1.3 Chronic ITP in Children

Between 15% and 20% of children, particularly those 10 years of age or older, may develop a chronic form of ITP that can resemble the disease in adults. The traditional cut-off point of six months may inadequately differentiate chronic from acute ITP in children, because a high rate of recovery was observed between six to 12 months in the Intercontinental Childhood ITP Study Group.

Therapeutic options for chronic ITP include supportive care and watchful waiting, IVIg, and anti-D immune globulin (in Rh+ non-splenectomized patients), and in refractory cases, splenectomy or immunomodulators. The optimally effective treatment of children with symptomatic chronic ITP is unknown, and there are few randomized controlled trials that have assessed the treatment options. The unpredictability of spontaneous recovery complicates the evaluation of treatment efficacy.

1.1.4 ITP in Adults

Adult ITP usually has an insidious onset without a preceding viral illness and is typically a chronic disease. Using a platelet concentration cut-off point of $50 \times 10^9/L$, an estimate of the incidence of ITP in Danish adults is 3.2 per 100,000 persons. Although ITP is thought to be more common in women of childbearing age, two studies have reported an increasing incidence with age.

In stable patients, the platelet count thresholds that are advocated for treatment range from $10 \times 10^9/L$ to $30 \times 10^9/L$. The therapy for patients who have platelets counts between $30 \times 10^9/L$ to $50 \times 10^9/L$ is individualized. In non-urgent situations, the first treatment is often corticosteroids with the addition of IVIg if platelets remain below $20 \times 10^9/L$ to $30 \times 10^9/L$. IVIg may also be used in patients who have contraindications to corticosteroids, in patients who are refractory to corticosteroids, or as part of the preparation for splenectomy or other surgery. Splenectomy is generally recommended within three to six months if a relapse occurs or if the disease is refractory to corticosteroids, IVIg, or anti-D immune globulin. A variety of drugs have been used in patients who are refractory to splenectomy, and no single treatment has been determined to be optimal in refractory ITP.

In patients with severe bleeding, IVIg may be used as part of multi-modal therapy. Emergency treatment may include intravenous corticosteroids, IVIg and anti-D immune globulin, vincristine, platelet transfusions, and factor VIIa.
1.2 Overview of Technology

Polyclonal IVIg is used as a replacement therapy in primary and secondary humoral immunodeficiencies and as an immunomodulatory therapy in autoimmune diseases and transplantation. Canada has one of the highest per capita consumption rates of IVIg in the world. This demand has grown at an average rate exceeding 10% since 2000.29 In 2004-2005, IVIg use per 1,000 persons varied across the provinces and territories, with the highest consumption in Alberta.30

IVIg is manufactured from large pools of plasma. In 2005, 24% of Canada’s IVIg supply came from voluntary donation of plasma in Canada. The remainder came from the plasma of paid donors in the US.31 The cost of IVIg per gram varies between C$55 to C$70, depending on the currency exchange rate.32 The cost of one infusion of 1 g/kg for a 70 kg adult is approximately $5,000, and the cost of a 0.5 mg/kg to 1.0 mg/kg infusion for a 20 kg child is $700 to $1,400.

IVIgs are available as four products through the Canadian Blood Services:

<table>
<thead>
<tr>
<th>Table 1: IVIgs available in the Canadian market</th>
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<tbody>
<tr>
<td><strong>Brand Name</strong></td>
</tr>
<tr>
<td>Gammagard-SD® and Gammagard Liquid (10%)</td>
</tr>
<tr>
<td>Gamunex™ 10%</td>
</tr>
<tr>
<td>IGIVnex™ 10%</td>
</tr>
<tr>
<td>Iveegam® EN</td>
</tr>
</tbody>
</table>

IVIgs=intravenous immunoglobulins.

In 1997-1998, a market shortage of IVIg occurred in countries that depended on US manufacturers. This was attributed to multiple factors, including increased demand, a limited supply, more stringent US regulatory requirements for plasma fractionation, and voluntary recalls of plasma products due to concerns about disease transmission and business practices.33,34 This IVIg shortage, with escalating costs and an increasing demand for off-label use, has prompted Canada and other countries such as the US and Australia to adopt new approaches to manage use.

In Canada, British Columbia and subsequently the Atlantic provinces have implemented an IVIg utilization program by developing guidelines, categorizing disorders into approved conditions or those requiring special approval, and providing a mechanism for the monitoring and regulating of off-label invalidated use.7,35 Other provinces and smaller regional centres are also developing strategies to best manage use.36 The National Advisory Committee on Blood and Blood Products (previously the Technical Working Group on Blood and Blood Products), an advisory group to the provincial and territorial deputy ministers of health, has been developing an interprovincial framework for IVIg utilization management and, with the Canadian Blood Services and an expert panel, has published evidence- and consensus-based guidelines for hematological and neurological indications.32,37
2 THE ISSUE

Canada has one of the highest per capita rates of consumption of IVIg in the world. The rate has been increasing annually over the past decade. Escalating cost, increasing demand for an expanding number of indications, and a recent IVIg shortage has prompted Canadians to adopt new approaches to manage IVIg use. Assessing the impact of IVIg in patients with ITP (an approved indication) and CIDP (an off-label indication) has been identified as a priority, given the high utilization rates for these indications in Canada. The highest use of IVIg occurs in the pediatric population with ITP. The potential availability of less costly alternative treatments for these conditions and the uncertainty of a therapeutic advantage of IVIg over alternative therapies constitute additional reasons for prioritizing this assessment in Canada. The focus of this report is on ITP. CIDP will be addressed in a future assessment.

3 OBJECTIVES

The objectives of the project were to determine the role of IVIg in the treatment of ITP by addressing the following research questions:

- Does IVIg have an incremental benefit in treating ITP over alternative standard therapy?
- What place does IVIg have in the management of acute or chronic ITP in children or adults?
- Is there sufficient evidence to identify subgroups of ITP patients who may preferentially benefit from IVIg?

4 CLINICAL REVIEW

4.1 Methods

A protocol was written a priori and followed throughout the review process.

4.1.1 Literature search strategy

A comprehensive search strategy was designed to identify primary studies on efficacy, effectiveness, and harms in ITP (Appendix 1). Because this is a small body of literature, no methodological restrictions were imposed. The databases searched were MEDLINE (1966 to December week 3, 2007), EMBASE (1980 to week 50, 2007), BIOSIS Previews (1990 to December 20, 2007), EconLit (searched August 2, 2006), and the TRIP Database (searched August 2, 2006). The following databases of The Cochrane Library were searched: CDSR, Central, HTA, and NHS EED (4th quarter 2007). Supplemental searching for epidemiology, standard care, and emerging treatment for ITP was undertaken in MEDLINE (1950 to January week 5, 2007). Supplemental searching for epidemiology, standard care, and emerging treatment for ITP was undertaken in MEDLINE (1950 to January week 5, 2007). Grey literature (literature that is not commercially published) was identified by searching the web sites of health technology assessment (HTA) and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. The US Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) web sites were searched for post-marketing surveillance on AEs. The proceedings of hematology conferences, including the
American Society of Hematology and the European Hematology Association; and neurology conferences, including the American Academy of Neurology, the American Neurological Association, and the Canadian Congress of Neurological Sciences; were searched (2006-2007). Two content experts in neurology were contacted as were the manufacturers and suppliers of IVIg in Canada (Talecris and Baxter) (Appendix 7).

The literature search (MEDLINE up to 2007 December week 3; Embase up to 2007 week 50; BIOSIS previews up to December 20, 2007) was updated on December 20, 2007, retaining the original search strategy to retrieve references for 2006-2007. The search for grey literature was similarly updated. In this instance, a list of health technology organizations and agencies used for all CADTH HTA searches was used. For a list of sources searched, go to http://www.cadth.ca.

### 4.1.2 Selection criteria

The criteria that were used to select studies are shown in Table 2.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials (full study reports*)</td>
<td>Patients of any age, other than neonates, with documented diagnosis of ITP, excluding those with associated conditions, except children with history of antecedent viral infection</td>
<td>Any preparation, source, dose, dosing regimen of IVIg included</td>
<td>IVIg: alternative doses or different preparations Corticosteroids: any dose, dosing regimen, route of administration Anti-D immunoglobulin Second line agents (immunomodulators) for chronic or refractory ITP (including combinations of agents) Splenectomy (for chronic ITP) Placebo Expectant management †</td>
<td>Overall mortality, mortality due to hemorrhage or treatment-related Other SAEs (e.g., intracranial hemorrhage), other major bleeding, treatment-related SAEs (e.g., thrombosis) Incidence of splenectomy For acute ITP, incidence of chronic ITP or recurrent ITP Quality of life measurements Minor bleeding Surrogate markers: platelet count‡</td>
</tr>
</tbody>
</table>

*Not abstract or conference proceeding  
†Close observation or watchful waiting, taking into account what is known about the natural history of the disease  
‡Regarding primary outcomes for acute childhood ITP, we considered reduction in clinically significant hemorrhage on any scale or grade as a continuous outcome or as an investigator- or patient-assessed proportionate outcome. For chronic ITP in children and adult ITP (which predominantly follows a chronic course), the proportion of patients with deferred splenectomy was the primary clinical outcome. Time to a platelet count ≥20×10^9/L or ≥50×10^9/L were additional primary outcomes in all ITP categories. Secondary efficacy outcomes included other platelet-related measures such as the proportion of patients achieving a platelet count ≥20×10^9/L at 24 hours, 48 hours, or 72 hours after treatment initiation.  
ITP=immune (idiopathic) thrombocytopenic purpura; IVIg=intravenous immunoglobulin; SAEs= serious adverse events.

### 4.1.3 Selection method

Screening was performed in two stages: (1) screening of the retrieved citations based on title and abstract and (2) full-text review of the potentially relevant citations. One reviewer (LP) independently screened titles and abstracts (if available) for relevancy. Exclusions at this level were screened by a second reviewer (MA) to verify. If there was uncertainty about relevance or if there was disagreement between reviewers, the citation was passed to the next level for full-text screening. Two reviewers (LP and MA) independently examined the full-text reports of the potentially relevant...
records, applying more stringent eligibility criteria, which had been developed a priori. Any discrepancies were resolved by consensus. There were no consequential conflicts between the two reviewers. A third level of screening was performed to exclude abstracts and conferences proceedings of trials, which provide insufficient data on study design and results to be used in analysis.

4.1.4 Data extraction strategy

One reviewer (MA) independently extracted data that were subsequently verified by another reviewer. Information included population characteristics at baseline (for example, mean age), study characteristics such as interventions (including dose and dosing regimen, source of IVIg), time points of assessment, and AEs (Appendix 2). The reviewers were not blinded to the study authors’ names or funding sources. Any discrepancies were resolved by discussion.

4.1.5 Strategy for validity assessment

As part of quality assessment, the validated Jadad scale was used.38 One reviewer (MA) independently performed quality assessment, which was subsequently verified by a second reviewer (AT). The Jadad scale is used to assess the methods for generating random assignments and double blinding and to determine whether there is a description of dropouts and withdrawals by intervention group. The scoring ranges from 1 to 5, with higher scores indicating higher quality. The allocation concealment was rated as adequate, inadequate, or unclear using the Schultz treatment allocation concealment questionnaire.39

4.1.6 Data analysis methods

The decision whether to perform a statistical pooling of individual studies was based on clinical and methodological judgment. For outcomes where a meta-analysis was deemed to be appropriate, quantitative data were extracted from trials using a standard data extraction form. For binary outcomes (for example, the proportion of patients with ITP who had a platelet count greater than or equal to 20×10⁹/L), relative risks (RRs) and 95% confidence intervals (CIs) were calculated for each study. For continuous outcomes (for example, mean number of days to a platelet count greater than or equal to 20×10⁹/L), the difference between study arms, its standard deviation (SD), and 95% CIs were calculated. Authors of the original studies were contacted for missing data that were needed for calculations. The meta-analyses were based on the random effects model of DerSimonian and Laird.40 A random effects model was consistently used, because some clinical and methodological diversity is inevitable even when the tests for statistical heterogeneity cannot detect it. For binary data, the estimates of pooled RR (with 95% CI) were calculated. A RR greater than 1 would indicate that more patients in the IVIg arm relative to the control or comparator arm developed a favourable outcome. For the aggregated continuous outcomes, we calculated weighted mean difference or standardized mean difference with respective 95% CIs. The degree of statistical heterogeneity across studies was assessed based on chi-square (χ²) and I² statistics. The I² expresses the percentage of between-study variability attributable to heterogeneity rather than sampling error. A value greater than 50% is considered to be substantial, whereas an I² of zero would indicate that all variability in effect estimates is due to sampling error in trials.41 The interpretation of heterogeneity estimates requires caution, especially when small numbers of trials are included. The statistical analyses in this review were performed using Review Manager 4.2 (The Cochrane Collaboration, Oxford, UK, 2006).
A conservative approach was taken to avoid bias in the estimates by not combining crossover and parallel trials. This decision was based on the methodological shortcomings of the identified crossover trials (for example, crossover based on the response to previous treatment rather than the original randomization). To avoid potential confounding, data from crossover trials were used only if the appropriate data for the pre-crossover phase of the trial were available.

Sensitivity analyses were planned to examine if the effect of IVIg varied across trial design and trial quality (for example, those with adequate allocation concealment). Preplanned subgroup analyses included the effect of treatment dose, mode of administration of corticosteroids, and special populations or settings (for example, refractory ITP). Differences in IVIg preparations were not considered in this review.

5 RESULTS

5.1 Quantity of Research Available

The literature search identified 1,577 potentially relevant reports (Appendix 3). A total of 907 reports were excluded based on title and abstract. Full-text screening with more stringent criteria was applied to 670 reports. Nine reports were unavailable, and 593 failed to meet inclusion criteria, leaving 77 reports. Of the 77 reports, 27 reports were subjected to a screening on the basis of pharmacoeconomics content. These will be assessed in an economic review of IVIg to appear in the fall of 2008. Of the 50 reports that were identified as relevant randomized controlled trials for the clinical review, 19 were not full study reports but abstracts or conference proceedings and were excluded, leaving 31 reports (242 citations were identified from an update literature search on December 20, 2007, but none met our inclusion criteria).

Of the 31 relevant randomized controlled trial publications for the clinical review, one was excluded because separate outcomes data were unavailable for each of the two randomized treatments.42 One report43 reported a post hoc subgroup analysis of another randomized controlled trial.44 One report45 identified itself as a preliminary analysis of Jacobs et al.’s study,46 and two reports47,48 were confirmed by the lead author to be preliminary analyses of the trial by Imbach et al.49 El-Alfy and Khalifa18 and Warrier et al.50 each reported two eligible trials. A few papers reported more than one trial, but only one was eligible for this review.51,52 Thus, of 31 included publications, 28 unique trials were identified for clinical review.

5.2 Acute Childhood ITP

Fifteen randomized controlled trials enrolled children with acute ITP,44,49-62 with most (11) comparing IVIg to corticosteroids. Two publications (Fujisawa and Khalifa) reported two trials each, but only one trial (“Study A”) in each report contained an IVIg arm and was eligible.51,52 Of the two trials reported by Warrier et al., one trial (“Study B”) enrolled older children with acute or chronic ITP and was not considered, because the results were not reported separately for acute ITP.50 Two trials had pharmaceutical industry funding,50,62 three were sponsored by non-governmental societies and foundations,43,44,53,54 and 10 did not report a funding source.49,51,52,55-61 The interventions analyzed in each trial are listed in Table 3.
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Intervention 3</th>
<th>Intervention 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette et al.</td>
<td>IVIg 1g/kg/day×2 (2 g/kg total)</td>
<td>prednisone oral 4 mg/kg/day×7, then tapered over 21 days</td>
<td>no treatment</td>
<td></td>
</tr>
<tr>
<td>Blanchette et al.</td>
<td>IVIg 1g/kg/day×2 (2 g/kg total)</td>
<td>prednisone oral 4 mg/kg/day×7, then tapered over 7 days</td>
<td>anti-D iv 25 μg/day×2 (Rh+ only)</td>
<td>IVIg 0.8 g/kg/day×1 (0.8 g/kg total)</td>
</tr>
<tr>
<td>Imbach et al.</td>
<td>IVIg 0.4 g/kg/day×5 (2 g/kg total)</td>
<td>prednisone oral 60 mg/m²/day×21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ancona et al.</td>
<td>IVIg 1 g/kg/day×1 to 2 (1 to 2 g/kg total)</td>
<td>methylprednisolone iv 30 mg/kg/day×2 to 3</td>
<td>methylprednisolone oral 30 mg/kg/day×7</td>
<td></td>
</tr>
<tr>
<td>Albayrak et al.</td>
<td>IVIg 0.5 g/kg/day×5 (2.5 g/kg total)</td>
<td>methylprednisolone oral 50 mg/kg/day×7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duru et al.</td>
<td>IVIg 0.8 g/kg/day×2 (1.6 g/kg total)</td>
<td>methylprednisolone oral 30 mg/kg/day×3 then 20 mg/kg/day×4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erduran et al.</td>
<td>IVIg 1 g/kg/day×2 (2 g/kg total)</td>
<td>methylprednisolone oral 30 mg/kg/day×3 then 20 mg/kg/day×4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujisawa et al. (Study A)</td>
<td>IVIg 1 g/kg/day×1 (repeat day 4 if platelets &lt;30) (1 to 2 g/kg total)</td>
<td>methylprednisolone iv 30 mg/kg/day×3</td>
<td>methylprednisolone iv 5 mg/kg/day×5</td>
<td>prednisolone oral 2 mg/kg/day×2 weeks, then tapering by day 21</td>
</tr>
<tr>
<td>Khalifa et al.</td>
<td>IVIg 0.4 g/kg/day×5 (2 g/kg total)</td>
<td>methylprednisolone iv 10 mg/kg/day×5</td>
<td>prednisone oral 2 mg/kg/day×4 weeks</td>
<td></td>
</tr>
<tr>
<td>Ozsoylu et al.</td>
<td>IVIg 0.4 g/kg/day×5 (2 g/kg total)</td>
<td>methylprednisolone oral 30 mg/kg/day×3 days then 20 mg/kg/day×4</td>
<td>prednisone oral 2 mg/kg/day×4 weeks</td>
<td></td>
</tr>
<tr>
<td>Rosthoj et al.</td>
<td>IVIg 1 g/kg/day×2 (2 g/kg total)</td>
<td>methylprednisolone iv 30 mg/kg/day×2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tarantino et al.</td>
<td>IVIg 0.8 g/kg/day×1 (0.8 g/kg total)</td>
<td>anti-D iv 75 μg/kg/day×1</td>
<td>anti-D iv 50 μg/kg/day×1</td>
<td></td>
</tr>
<tr>
<td>Benesch et al.</td>
<td>IVIg 1 g/kg/day×2 (2 g/kg total)</td>
<td>IVIg 0.3 g/kg/day×2 (0.6 g/kg total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warrier et al. (Study A)</td>
<td>IVIg 0.5 g/kg/day×2 (1 g/kg total)</td>
<td>IVIg 0.25 g/kg/day×2 (0.5 g/kg total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burdach et al.</td>
<td>7S IVIg 0.4 g/kg/day×5 (2 g/kg total)</td>
<td>5S IVIg 0.4 mg/kg/day×5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5S IVIg=various preparations of IVIg, in which the fragment crystallizable portion was partly removed; 7S IVIg=various preparations of IVIg, in which the fragment crystallizable portion was presented; iv=intravenous; ITP=immune (idiopathic) thrombocytopenic purpura; IVIg=intravenous immunoglobulin; Rh+=rhesus positive.
a) Trial characteristics
The characteristics of each trial are presented in Appendix 5 Table 1. All trials were parallel group trials. After initial (randomized) treatment, five trials used a conditional crossover of patients to the other treatment(s), for lack of a specified response or relapse to a specified platelet count.44,49,57,58,61 A response-conditional re-treatment with the same intervention was also given in six trials.49,50,52,53,55,62 In two trials, a higher dose of IVIg was used in re-treatment.50 Trial follow-up or observation periods ranged from nine days60 to one year.55

b) Study population
Across studies, participants’ ages ranged from one month to 18 years (Appendix 5 Table 1). One trial did not report an age inclusion criterion,60 and one trial did not limit the criterion to a minimum age.49 Inclusion of a proportion of patients with neonatal alloimmune or autoimmune thrombocytopenia could not be ruled out in four of 15 trials that included patients aged two months or younger or did not report a minimum age inclusion criterion.49,52,58,60

Nine trials enrolled children who had platelet counts less than or equal to 20×10^9/L.44,51,53-57,61,62 One trial included exclusively patients who had a platelet count of less than 10×10^9/L.51 Other platelet count inclusion criteria included less than 25×10^9/L50 less than or equal to 30×10^9/L49,60 or less than 50×10^9/L.59 Two trials had dichotomous platelet count inclusion criteria based on patients’ bleeding status (Appendix 5 Table 1).50,52

No trial restricted eligibility criteria to children with clinically significant hemorrhage, although a few trials specified the presence of wet purpura for at least a portion of participants or grouped patients by the type of purpura (Appendix 5 Table 1).44,52,56,60,62 Several trials excluded those with serious or life-threatening bleeding. This is consistent with recommendations to use multimodal treatment for such events.

Nine trials reported the inclusion of newly diagnosed or untreated patients with acute ITP.44,49,52,53,55,56,59,60,62 Two trials defined acute ITP as being of less than three months’ duration.50,60 Diagnostic criteria were not reported or were not comprehensive enough to exclude secondary ITP in five trials.49,56,57,60,62

c) Outcomes
All 15 trials stated or implicitly presented platelet count as the primary efficacy outcome measure (Appendix 5 Table 1). Clinical efficacy was not examined in any trial except one in which the reduction in gross internal hemorrhage (gastrointestinal bleed and hematuria) was assessed and another that reported “serious bleeding.”52,56 Platelet-count-related outcomes were used to measure the rapidity of response as time to a certain count52-54,61 or the proportions of patients achieving a specified count at a specified time.47-50,52-61 Duration or sustainability of platelet response was not commonly reported. AE reporting was incomplete in most trials.

d) Study quality
The Jadad score for the 15 trials ranged from 1 to 3, with one trial scoring 3/5.49 Nine trials had a Jadad score of 1,44,51,53-55,57,59,60 and five trials had a Jadad score of 2.50,54,58,61,62 The Schulz allocation concealment was considered to be adequate for four trials34,52-54 and unclear for the rest (Appendix 5 Table 2). Limitations of the internal validity of each trial are summarized in Appendix 5 Table 2.
5.2.1 Data analyses and syntheses

a) IVIg versus corticosteroids

Efficacy

Regardless of the type, dose, and mode of administration of corticosteroids or IVIg, five of the six non-crossover trials that compared IVIg with oral or intravenous corticosteroids demonstrated significantly fewer days with platelet counts less than 30×10^9/L or less than 50×10^9/L, higher mean platelet counts in the first week of therapy with IVIg compared with corticosteroids, or a higher proportion of patients with platelet counts greater than or equal to 20×10^9/L at 24 hours and 48 hours. Two trials did not demonstrate any significant efficacy differences. Trials allowing a conditional crossover of patients failed to show a significant efficacy advantage of any intervention or demonstrated IVIg superiority. Thus, across parallel and response-conditional crossover designs, five of 11 relevant trials suggested IVIg (total dose 0.8 g/kg to 2 g/kg) showed superior efficacy. Of these, four trials found a trend of statistical significance favouring IVIg in the improvement of thrombocytopenia when compared with oral prednisone (2 mg/kg to 4 mg/kg), but did not demonstrate superiority of IVIg when compared with a higher dose of intravenous methylprednisolone (30 mg/kg), unlike two other trials using lower doses of methylprednisolone (5 mg/kg).

Six trials (parallel and response-conditional crossover designs) failed to show a significant result in favour of IVIg (total dose 1.6 g/kg to 2.5 g/kg) or corticosteroid. Of these, one trial examined a low corticosteroid dose (60 mg/m^2). The remainder observed similar efficacies of IVIg compared with higher doses of oral prednisone (30 mg/kg to 50 mg/kg) or intravenous methylprednisolone (10 mg/kg). One of the six trials demonstrated a statistically significant efficacy advantage of IVIg compared with a low corticosteroid dose (oral prednisone) but not compared with a higher dose of intravenous methylprednisolone. Another trial showed a statistically significantly shorter mean time to a platelet count greater than 20×10^9/L (IVIg 2.9 days versus oral methylprednisolone 4.1 days) and proportion of patients with a platelet count greater than 20×10^9/L on day 2 (IVIg 86%, oral methylprednisolone 50%) even when it failed to do so on other platelet-related outcome measures (Appendix 5 Table 2).

Primary outcomes

Reduction in bleeding: Data synthesis was not allowed for this outcome, because of the differences between trials regarding characteristics, insufficient data, and the poor quality of the studies. Conclusions could not be drawn about the relative efficacy of IVIg and corticosteroids for the control of bleeding.

One trial reported data for five patients with gastrointestinal hemorrhage (4) or hematuria (1). All had diminished bleeding by day 4 regardless of treatment. Another trial reported no “serious bleeding” with IVIg or methylprednisolone in patients who did not have major clinical bleeding at baseline.
Intracranial hemorrhage was not a specified outcome in any trial and was not systematically investigated. Five trials that included a corticosteroid comparison reported on ICH. Erduran et al. reported zero cases of ICH in 46 patients treated with IVIg or corticosteroids during a follow-up of up to six months. Two trials reported one case each of ICH in patients who were initially treated with corticosteroids (oral methylprednisolone 50 mg/kg/day, prednisone 2 mg/kg/day). Both improved after multi-modality treatment. One fatal CNS hemorrhage occurred in a patient with a "florid viral infection" who initially received IVIg (three doses of 0.4 mg/kg/day) and subsequently corticosteroids. Another trial reported an ICH event in a patient approximately three months after enrolment in the study. The patient was initially randomized to receive anti-D immunoglobulin 75 μg/day, did not respond, and was then treated with IVIg and corticosteroids. Given the rarity of events and the potential validity issue for one trial, qualitative and quantitative syntheses for ICH were not possible.

One other life-threatening bleeding event (retinal hemorrhage and melena) was reported in the included trials. This event occurred 11 months post diagnosis in a patient who developed chronic ITP after being unresponsive to methylprednisolone and subsequent treatment with IVIg.

**Time to platelet count greater than or equal to 20×10^9/L and greater than or equal to 50×10^9/L:**

Three trials reported time to platelet count greater than or equal to 20×10^9/L and greater than or equal to 50×10^9/L. One additional trial reported only days to a platelet count greater than or equal to 50×10^9/L (Appendix 5 Table 2). Outcomes were reported as means, medians, or both. Data could not be combined for means, because the estimates of dispersion were unavailable for one of the two relevant studies. We did not undertake a quantitative analysis of data for medians, because there is a lack of consensus about the optimal methodological approach to combining medians.

Regardless of IVIg dosage and corticosteroid dose or mode of administration, three of the four trials found significant results in favour of IVIg for at least one of the two outcomes. Blanchette et al. reported a statistically significant difference in the mean time to platelet count greater than or equal to 20×10^9/L when oral prednisone 4 mg/kg/day was compared with a total IVIg dose of 0.8 g/kg but not a higher dose of 2 g/kg (2.6 days versus 1.4 days versus 2.9 days). The median times were not significantly different. Another trial reported a significantly shorter median time to a platelet count greater than or equal to 20×10^9/L when IVIg (2 g/kg total dose) was compared with oral prednisolone 4 mg/kg/day. Both interventions were significantly better than no treatment (two days versus one day versus four days). Erduran et al. reported that IVIg 2 g/kg significantly shortened the mean time to a platelet count of greater than or equal to 20×10^9/L when compared with oral methylprednisolone 30 mg/kg/day (2.9 days versus 4.1 days). The mean time to a platelet count of greater than or equal to 50×10^9/L was not significantly different (5.0 days versus 5.2 days). In Fujisawa et al.'s study, there was a significantly shorter median time to a platelet count greater than or equal to 50×10^9/L when IVIg (total 1 g/kg) was compared with oral prednisolone 2 mg/kg/day (two days versus four days) but not when compared with higher corticosteroid doses (intravenous methylprednisolone 5 mg for three days or 30 mg/kg/day for three days).

**Secondary outcomes**

*Proportion of patients with platelet count greater than or equal to 20×10^9/L at 24 hours, 48 hours, and 72 hours:* Sufficient data were available to conduct meta-analyses on the secondary outcomes (proportion of patients with platelet counts greater than or equal to 20×10^9/L at 24 hours, 48 hours, or
All included trials enrolled patients with platelet counts of less than or equal to $20 \times 10^9/L$. None of the data was affected by the conditional crossover of patients (Appendix 5 Table 2). One trial had two IVIg arms (total doses 2 g/kg and 0.8 g/kg), and the data were combined.\textsuperscript{53}

For the time point of 24 hours, data were available from four reports\textsuperscript{44,53,54,56} and obtained from the authors of a fifth trial\textsuperscript{57} (total evaluable number=289). When combining data from the five trials regardless of IVIg dose, corticosteroid subtype, dose, and mode of administration, the pooled relative risk for achieving a platelet count greater than or equal to $20 \times 10^9/L$ at 24 hours was 1.55 (95% CI: 1.19; 2.03), in favour of IVIg (Appendix 4 Figure 1). In subgroup analyses, a statistically significant difference was observed when IVIg was compared with lower dose corticosteroids (4 mg/kg prednisone) (RR 1.84, 95% CI: 1.18; 2.87) but not a higher dose\textsuperscript{44,56,57} or intravenous corticosteroids.\textsuperscript{44,56} A sensitivity analysis on trials with adequate allocation concealment produced a RR of 1.59 (95% CI: 1.15; 2.19).\textsuperscript{44,53,54} Table 4 summarizes these results with data from the 48-hour and 72-hour time points.

At 48 hours, data were available for five trials (total evaluable number=290).\textsuperscript{53,54,56,57,61} The overall RR of achieving a count greater than or equal to $20 \times 10^9/L$ at 48 hours was 1.34 (95% CI: 1.15; 1.56) in favour of IVIg (Appendix 4 Figure 2). Subgroup analyses and sensitivity analyses are summarized in Table 4.

Four trials reported the proportion of patients with platelet counts greater than or equal to $20 \times 10^9/L$ at 72 hours (total evaluable number=246).\textsuperscript{53,54,56,57} The overall RR of achieving a count greater than or equal to $20 \times 10^9/L$ at 72 hours was 1.17 (95% CI 1.06; 1.30) in favour of IVIg (Appendix 4 Figure 3). Subgroup and sensitivity analyses appear in Table 4.

### Table 4: Relative risk of platelet count greater than or equal to $20 \times 10^9/L$ at 24 hours, 48 hours, or 72 hours for IVIg versus corticosteroids

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
<th>24 Hours</th>
<th>48 Hours</th>
<th>72 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIg versus corticosteroids</td>
<td>1.55 (1.19, 2.03)</td>
<td>1.33 (1.14, 1.55)</td>
<td>1.17 (1.06, 1.30)</td>
</tr>
<tr>
<td>5 trials\textsuperscript{44,53,54,56,57} N=289</td>
<td>5 trials\textsuperscript{44,53,54,56,57} N=288</td>
<td>4 trials\textsuperscript{44,53,54,56,57} N=246</td>
<td></td>
</tr>
<tr>
<td>IVIg versus lower-dose corticosteroids</td>
<td>1.84 (1.18, 2.87)</td>
<td>1.34 (1.10, 1.63)</td>
<td>1.18 (1.03, 1.35)</td>
</tr>
<tr>
<td>2 trials\textsuperscript{53,54} N=145</td>
<td>2 trials\textsuperscript{53,54} N=145</td>
<td>2 trials\textsuperscript{53,54} N=101</td>
<td></td>
</tr>
<tr>
<td>IVIg versus higher-dose corticosteroids</td>
<td>1.41 (1.00, 1.97)</td>
<td>1.31 (1.00, 1.72)</td>
<td>1.14 (0.88, 1.47)</td>
</tr>
<tr>
<td>3 trials\textsuperscript{44,56,57} N=144</td>
<td>3 trials\textsuperscript{56,57,61} N=143</td>
<td>2 trials\textsuperscript{56,57} N=101</td>
<td></td>
</tr>
<tr>
<td>IVIg versus intravenous corticosteroids</td>
<td>1.40 (0.99, 1.98)</td>
<td>1.25 (0.89, 1.76)</td>
<td>1.13 (1.01, 1.28)</td>
</tr>
<tr>
<td>2 trials\textsuperscript{44,56} N=120</td>
<td>1 trial\textsuperscript{56} N=77</td>
<td>3 trials\textsuperscript{53,54,57} N=169</td>
<td></td>
</tr>
<tr>
<td>IVIg versus oral corticosteroids</td>
<td>1.59 (1.15, 2.19)</td>
<td>1.39 (1.16, 1.67)</td>
<td>1.18 (1.03, 1.35)</td>
</tr>
<tr>
<td>3 trials\textsuperscript{44,53,54} N=188</td>
<td>3 trials\textsuperscript{53,54,61} N=187</td>
<td>2 trials\textsuperscript{53,54} N=145</td>
<td></td>
</tr>
<tr>
<td>Trials with adequate allocation concealment</td>
<td>1.59 (1.15, 2.19)</td>
<td>1.39 (1.16, 1.67)</td>
<td>1.18 (1.03, 1.35)</td>
</tr>
<tr>
<td>3 trials\textsuperscript{44,53,54} N=188</td>
<td>3 trials\textsuperscript{53,54,61} N=187</td>
<td>2 trials\textsuperscript{53,54} N=145</td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence intervals; IVIg=intravenous immunoglobulin; N=number of participants; RR=relative risk.
Proportion of patients with platelet count less than or equal to \(150 \times 10^9/L\) at six-month follow-up:

Nine trials considered this outcome.\(^4\),\(^44\),\(^49\),\(^52\),\(^54\),\(^57\)-\(^59\),\(^61\) One of these trials provided chronicity data after 11 months of observation\(^58\) instead of the six months used in the other trials. Jadad scores ranged from 1\(^44\),\(^52\),\(^59\) to 3.\(^49\) Four trials had adequate allocation concealment,\(^44\),\(^52\)-\(^54\) and the remainder were unclear (Appendix 5 Table 2). One trial administered two different doses of IVIg,\(^53\) and another trial used three different corticosteroid regimens.\(^52\) For these two trials, data were combined for the drug class. Six trials enrolled participants with platelet counts less than or equal to \(20 \times 10^9/L\)\(^49\),\(^44\),\(^54\),\(^53\),\(^57\),\(^61\) Ozsoy\, et al.'s trial included patients with a platelet count of less than or equal to \(50 \times 10^9/L\),\(^59\) and Fujisawa et al. included patients with platelet counts up to \(29 \times 10^9/L\).\(^52\) We excluded chronicity data from five studies that were likely to have been influenced by response-conditional (non-randomized) crossover of a proportion of participants.\(^49\),\(^44\),\(^57\),\(^58\),\(^61\) Thus, relevant data from four studies were combined (total evaluable number=282).\(^52\)-\(^54\),\(^59\) No significant difference was observed between IVIg and corticosteroids for incomplete recovery or “chronicity” at six months RR 0.94 (95% CI 0.54; 1.66) (Appendix 4 Figure 4).

Adverse events

Comparative qualitative or quantitative harms analyses of relevant trials were not possible, because of incomplete AE reporting. None of the trials reported total adverse events (TAEs), total serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs) across the treatment arms. Appendix 5 Table 2 summarizes the reported AEs related to each intervention in the included trials. Commonly reported IVIg infusion-related AEs were headache, vomiting, fever and chills, meningismus and aseptic meningitis, and rash.\(^44\),\(^49\),\(^52\)-\(^54\),\(^57\)-\(^59\),\(^61\) Commonly reported corticosteroid-related AEs were increase in body weight, cushingoid features, dyspepsia, glycosuria, hypertension, headache, and behavioural changes.\(^44\),\(^49\),\(^52\),\(^54\),\(^57\),\(^58\),\(^61\)

Of the six trials\(^51\)-\(^54\),\(^56\),\(^59\) that did not allow a conditional crossover of participants to the other treatment, three\(^52\),\(^54\),\(^59\) reported the proportions of patients with treatment-related AEs: 9% to 30% of patients receiving IVIg experienced transient infusion-related AEs such as nausea, vomiting, fever, chills, and headaches, while 0% to 13% experienced corticosteroid-related AEs. All five trials that allowed some patients to crossover to the other treatment reported the proportions of patients who had at least one treatment-related AE.\(^44\),\(^49\),\(^57\),\(^58\),\(^61\) One of these trials reported pre-crossover adverse event data by intervention arm: IVIg 61% versus corticosteroids 20%.\(^44\) In the other trials, 13% to 41% of patients who received IVIg and 77% to 100% of patients who received corticosteroids experienced at least one AE.\(^49\),\(^57\),\(^58\),\(^61\) No trials reported thrombotic events or infectious complications.

Subgroup analysis

Studies did not grade hemorrhage to distinguish the clinical severity of the disease. No trial exclusively focused on patients with clinically major hemorrhage.

Heegaard et al.\(^43\) conducted a post hoc subgroup analysis of another trial (Appendix 5 Tables 1 and 2)\(^44\) in which six children with acute childhood ITP that was associated with current or recent parvovirus B19 infection were compared with 41 children who did not have parvovirus B19 infection. No statistically significant differences were observed in the rates of chronicity beyond six months when the parvovirus B19 positive group was compared with the parvovirus B19 negative group. Of the six children with parvovirus B19 infection, three children who received IVIg achieved normal platelet counts by eight weeks whereas all three children who received high dose corticosteroids progressed to chronicity, suggesting differential response rates to each treatment.
These findings, however, are hypothesis-generating only. In this post hoc analysis, there was a high probability of type II error.

**b) IVIg versus anti-D immunoglobulin**

**Efficacy**

Two trials compared IVIg [in Rh+, or Rh+ and rhesus negative (Rh−) patients] with anti-D immunoglobulin in Rh+ patients (total evaluable number=208). Reduction in hemorrhage was not a predefined outcome in either trial. Time to platelet counts greater than or equal to 20×10⁹/L and greater than or equal to 50×10⁹/L were measured in one trial.53

Blanchette et al. compared total doses of 0.8μg/kg and 2μg/kg of IVIg with a total dose of 50 μg/kg of anti-D immunoglobulin (given as 25 μg/kg/day for two days).53 Two randomizations were used based on rhesus status. Participants were randomized to be in the anti-D immunoglobulin arm only if they were Rh+ but were randomized to be in all other groups regardless of Rh status, resulting in the anti-D immunoglobulin group differing systematically from the IVIg groups (Appendix 5 Tables 1 and 2). Differences in treatment responses associated with this systematic difference cannot be ruled out, no matter how unlikely. IVIg was superior to anti-D immunoglobulin in reducing the number of days with platelet counts less than or equal to 20×10⁹/L or less than or equal to 50×10⁹/L. After correction for multiple comparisons, the difference between IVIg 0.8 g/kg and anti-D immunoglobulin remained significant. The rates of retreatment were similar. Tarantino et al. compared single doses of anti-D immunoglobulin 75 μg/kg and 50 μg/kg with 0.8 g/kg of IVIg and permitted re-treatment (same intervention) of non-responders. Tarantino et al. concluded that IVIg 0.8 g/kg and anti-D immunoglobulin 75 μg/kg have equivalent efficacy, but that of anti-D 50 μg/kg is lower. The likelihood of achieving a platelet count greater than or equal to 20×10⁹/L at 24 hours was significantly different and in favour of IVIg and anti-D immunoglobulin 75 μg/kg when compared with anti-D immunoglobulin 50 μg/kg. This difference was lost at later time points.62 One case of ICH was reported in the 32 patients who had received anti-D immunoglobulin 75 μg/kg and no cases in the other treatment arms (total incidence 1/101). The patient bled at day 98 after being unresponsive to anti-D immunoglobulin and IVIg and partially responsive to corticosteroids.

Acknowledging the limitation of internal validity for Blanchette et al.’s study53 in terms of rhesus status, we undertook the only meta-analysis that was possible for one of the secondary outcomes after we estimated data from figures in the two reports. Regardless of IVIg and anti-D immunoglobulin dosages, the pooled RR for the proportion of patients with platelet count greater than 20×10⁹/L at 24 hours was 1.52 (95% CI: 0.92; 2.52) for a pooled sample size of 208 patients (Appendix 4 Figure 5).

**Adverse events**

The reporting of AEs was selective and heterogeneous for the two trials, precluding any quantitative synthesis. There was no reporting of TAEs or SAEs by treatment groups. Reported treatment-related AEs included headache, fever, nausea, and vomiting with IVIg and anti-D immunoglobulin and reduction in hemoglobin with anti-D immunoglobulin.

In Blanchette et al.’s trial,53 a significantly higher incidence of fever, nausea, vomiting, and headache was observed in patients who were randomized to receive a total IVIg dose of 0.8 g/kg (16%) or 2 g/kg (18%) compared with anti-D immunoglobulin (3%). Proportionally more patients treated with anti-D immunoglobulin had a hemoglobin concentration below 6.2 mmol/L (24%) compared with
IVIg (6% to 12%), with a nadir occurring at seven to 14 days (Appendix 5 Table 2). A p-value was not reported to assess the statistical significance.

Estimates from Tarantino et al.’s graphical presentation of data indicated a non-significant smaller reduction in mean hemoglobin in the IVIg group compared with 75 μg/kg or 50 μg/kg of anti-D immunoglobulin in the first week.62 There was no significant difference between IVIg and anti-D immunoglobulin in the percentages of patients experiencing other common treatment-related AEs, although headache was reported as more severe with IVIg.62 This study differed from Blanchette et al.’s study53 because it used routine pre-infusion medication with diphenhydramine and acetaminophen for both infusions. Despite this premedication, Tarantino et al. did not report lower percentages of patients experiencing AEs. The two studies also differed in that Blanchette et al.53 used a lower daily dosage of anti-D immunoglobulin and a higher total dosage of IVIg in one of the two IVIg arms.

c) **IVIg versus placebo or expectant management**

There were no placebo-controlled trials. Blanchette et al. compared IVIg with close observation (evaluable number=35).54 Significant differences favouring IVIg were noticed for several platelet-associated outcome measures of early recovery, including time to platelet counts greater than or equal to 20×10^9/L and greater than or equal to 50×10^9/L. The reduction in hemorrhage, however, was not assessed. Only drug-related AEs were reported, precluding relative harms analyses (Appendix 5 Table 2). It was reported that 75% of children who received IVIg had one or more symptoms of nausea, vomiting, fever, and headache.

d) **IVIg in different doses or preparations**

Three trials compared different doses of IVIg (total evaluable number=111).50,53,55 Total higher doses ranged from 1 g/kg to 2 g/kg and lower doses from 0.5 g/kg to 0.8 g/kg (Table 4, Appendix 5 Tables 1 and 2). The three trials used different IVIg preparations that may vary in IgG content and other characteristics. All three trials allowed the retreatment of non-responders.

**Efficacy**

Although the authors of two of the three trials concluded that lower and higher IVIg dosages are equivalent in effecting early improvement in thrombocytopenia, the trials were not of non-inferiority or equivalency design.50,53 The third trial by Benesch et al.55 found that a total dose of 2 g/kg was superior to 0.6 g/kg based on day 3 median platelet counts (103×10^9/L versus 50×10^9/L).

Of the three trials, Blanchette et al.’s trial53 had the largest evaluable patient population (number=69). Furthermore, it investigated the highest of the lower IVIg doses in the three trials (0.8 g/kg). Because Warrier et al.50 permitted higher baseline platelet counts as an inclusion criterion, we estimated relevant data from the graphical presentation for children with baseline counts less than 20×10^9/L (number=8). Quantitative syntheses were undertaken for two secondary outcomes. A significant difference in efficacy was not detected between higher and lower doses of IVIg, based on the proportion of patients achieving a platelet count greater than or equal to 20×10^9/L at 48 hours and 72 hours. Given the risk estimate and narrow CIs around 1.0 in the 48-hour and 72-hour meta-analyses [RR 0.95 (95% CI 0.80 to 1.14) and RR 1.01 (95% CI 0.84 to 1.21) respectively], any difference between efficacies is likely to be small (Appendix 4 Figures 6 and 7).
One small randomized controlled trial (evaluable number=20)\(^{60}\) compared intact (7S) IgG to a 5S F(ab); fragment in which a portion of the fragment crystallizable (Fc) had been removed. Reduction in hemorrhage and time to platelets greater than or equal to 20×10\(^9\)/L were not assessed. The time required to reach a platelet count greater than 50×10\(^9\)/L at day 3 was eight of 10 patients in the IVIg 7S group, while it was two of 10 in the 5S group (p<0.01). The proportion of patients achieving a platelet count of >100×10\(^9\)/L within four days of therapy was greater in the group receiving IVIg 7S, as was the mean platelet count at nine days, consistent with current theories of the role of Fc in the mechanism of action of IVIg. The comparator (5S IVIg) is not regarded as a standard of treatment.

**Adverse events**

No trial reported total SAEs, TAEs, or total WDAEs by treatment. Blanchette et al. did not report drug-related AEs separately for the two IVIg dosages, except for the percentages of patients with a drop in hemoglobin below 6.2 mmol/L in the 7 to 14 days after treatment. These were 12% of patients who received a total dose of 2 g/kg versus 6% of patients who received 0.8 g/kg IVIg.\(^{53}\) Warrier et al. did not find a significant difference in the incidence of infusion-related AEs in 12 children with acute ITP, all younger than five years old, who were treated with 1 g/kg versus 0.5 g/kg IVIg (total dose).\(^{50}\) In contrast, Benesch et al. observed a significantly higher incidence of total treatment-related AEs with 2 g/kg compared with 0.6 g/kg (41% versus 12%).\(^{55}\) The latter two trials differed in that Warrier et al. allowed pre-infusion medication, and their higher dose was half that of the highest dose in Benesch et al.’s study.

### 5.3 Chronic Childhood ITP

Four trials (in three reports) enrolled exclusively children with chronic ITP and compared IVIg with corticosteroids or anti-D immunoglobulin.\(^{17,18,25}\) El Alfy and Khalifa conducted two separate trials. The first trial compared one dose of IVIg 0.8 g/kg with intravenous methylprednisolone 10 mg/kg/day for three days (Study A), and the second study compared three treatments given every four to six weeks for a maximum of 12 cycles: IVIg 0.25 g/kg/day for two days, oral methylprednisolone 4 mg/kg/day for four days, and one dose of anti-D 50 μg/kg (Study B).\(^{18}\) No trials compared IVIg with placebo or no treatment.

#### a) **Trial characteristics**

The four trials were open-label parallel group randomized controlled trials conducted in Egypt\(^{18,25}\) or Sweden\(^{17}\) (Appendix 5 Table 3). Each trial was confounded by additional non-randomized treatment. Only the Swedish trial reported funding from non-pharmaceutical agencies. Three trials permitted response-conditional crossover (of refractory patients) from one treatment arm to the other\(^{17}\) or from a corticosteroid arm to IVIg or anti-D immunoglobulin.\(^{18}\) The fourth trial permitted maintenance therapy (re-treatment) of a subset of patients in the anti-D immunoglobulin group without specifying the indication or basis for selection of this subset.\(^{25}\) The follow-up for relevant outcomes ranged from four weeks\(^{25}\) to five years.\(^{17}\) The number of evaluable patients ranged from 14 to 34 for the relevant comparisons.

#### b) **Study population**

All patients had thrombocytopenia for more than six months and had not undergone splenectomy. One trial reportedly ensured that included patients were not on any concomitant treatment.\(^{17}\) No trial included patients exclusively with clinically important bleeding.
c) Outcomes
One trial reported total drug-related AEs as a proportion of patients with at least one AE.\textsuperscript{17} This was also the only trial that reported specific AEs by treatment arms, permitting relative safety analysis. No trial reported TAEs and total WDAEs by treatment arms. In one trial, an SAE of ICH was reported in a patient on IVIg before the start of trial medication.\textsuperscript{25}

No trial reported the primary outcomes of time to platelet count greater than or equal to $20\times10^9$/L and greater than or equal to $50\times10^9$/L. Three trials reported the other primary outcome of deferred splenectomy.\textsuperscript{18,25} All trials estimated efficacy on platelet-related endpoints, and three also incorporated the clinical endpoints of hemorrhage.\textsuperscript{18,25}

d) Study quality
No trial reported adequate allocation concealment, and Jadad scores were 1\textsuperscript{18,25} or 2.\textsuperscript{17} Trials were confounded by additional non-randomized treatments. Hedlund-Treutiger’s trial\textsuperscript{17} allowed (platelet) response-conditional crossover to the other treatment at the patients’ discretion. Efficacy and harms data were confounded by this non-randomized crossover treatment exposure and its inherent period and carryover effects.\textsuperscript{17}

El Alfy \textit{et al.} recommended additional doses of anti-D immunoglobulin every three to four weeks to a subset of patients (67\%) in the anti-D immunoglobulin group, but it is unclear why. Data pertaining to the outcome of splenectomy was limited to this sample subset. The randomization process for El Alfy \textit{et al.}’s study was unclear because Rh status was not a reported criterion for enrolment, although all patients who received anti-D immunoglobulin were Rh+, suggesting assignment on the basis of Rh status rather than true randomization.\textsuperscript{25}

In El Alfy and Khalifa’s two trials, gastrointestinal bleeding associated with corticosteroid use prompted (non-randomized) reassignment to IVIg in Study A and to IVIg or anti-D immunoglobulin in Study B.\textsuperscript{18} This non-randomized crossover confounded data associated with steroid arms in the two trials.

5.3.1 Data analyses and syntheses

a) IVIg versus corticosteroids
Three trials compared IVIg with corticosteroids.\textsuperscript{17,18} Quantitative data syntheses could not be undertaken, because of the non-randomized crossover confounding and loss of independence of crossover data.

Efficacy
All three trials lacked inferential statistical analyses. Given the questionable internal validity of the highlighted trials, evidence synthesis was not undertaken. Hedlund-Treutiger \textit{et al.} (evaluable number=23) concluded that IVIg was superior for a short-term response (improvement in platelet count on day 3 of the first cycle) whereas long-term improvement in platelet counts (over at least three months without therapy) was more favourable with oral dexamethasone cyclical treatment (Appendix 5 Table 4).\textsuperscript{17}

In their two trials (evaluable number=16 and 14), El Alfy \textit{et al.} concluded that IVIg was insignificantly better than corticosteroid in improving platelet counts, reducing severe bleeding episodes and days of severe bleeding, and deferring splenectomy.\textsuperscript{18}
Adverse events
Two trials (in one report) did not report AE data by treatment groups.\textsuperscript{18} Hedlund-Treutiger \textit{et al.} reported similar number of patients experiencing AEs for the two interventions. Appendix 5 Table 4 summarizes the reported AEs.

\textbf{b) IVIg versus anti-D}

\textbf{Efficacy}
The proportion of patients with deferred splenectomy was similar across interventions in one trial\textsuperscript{18} and reported only for a subset of patients in the anti-D immunoglobulin treatment arm in the other.\textsuperscript{25}

Adverse events
One of the two trials in El Alfy and Khalifa’s report (evaluable number=15) and another by El Alfy \textit{et al.} (evaluable number=34) compared IVIg with anti-D immunoglobulin.\textsuperscript{18,25} Neither trial reported AEs by treatment arms, precluding harms analysis (Appendix 5 Table 4). Inferential statistics were lacking in one report.\textsuperscript{18} Different ways of reporting outcomes and issues of study quality precluded any quantitative or qualitative data syntheses.

\textbf{5.4 ITP in Adults}

Seven randomized controlled trials were included. One report\textsuperscript{45} was a preliminary analysis of another.\textsuperscript{46} Appendix 5 Table 5 gives an overview of the trials, including interventions, comparators, patient population, trial country, and funding sources.

\textbf{Study characteristics}
Six of the seven trials were open-label. The two double-blind trials compared new IVIg preparations with regular IVIg in identical doses.\textsuperscript{63,64} One trial used a factorial design.\textsuperscript{65} No trial permitted patient crossover. Two parallel trials provided additional booster treatments to pre-defined non-responder, partial responder, or relapsing patients.\textsuperscript{66,67} The number of randomized patients in the trials ranged from 20\textsuperscript{66} to 122.\textsuperscript{65} Except for 1 three-armed trial,\textsuperscript{46} all trials had two treatment arms.

\textbf{Study population}
Two trials enrolled adults with newly diagnosed and untreated ITP,\textsuperscript{46,65} four trials were restricted to patients with established chronic ITP (greater than six months duration),\textsuperscript{63,64,66,68} and one trial included a mixture in which there was a minority (16\%) of patients with acute ITP\textsuperscript{67} (Appendix 5 Tables 5 and 6). No trial examined patients with clinically important hemorrhage in particular. No trials enrolled pregnant women with ITP.

\textbf{Interventions}
The seven trials compared four interventions (Appendix 5 Table 5): two trials examined IVIg versus corticosteroid in 146 randomized or evaluable patients;\textsuperscript{46,65} one trial compared IVIg with IVIg plus corticosteroid in 26 evaluable patients;\textsuperscript{46} three trials assessed different IVIg doses in 84 randomized patients;\textsuperscript{66-68} and two trials investigated regular versus modified IVIg in 60 randomized patients.\textsuperscript{63,64}

\textbf{Outcomes}
All seven trials examined efficacy in terms of platelet-related outcomes. The mean and median times to platelet count greater than 50×10\textsuperscript{9}/L was reported in four trials.\textsuperscript{63,64,66,68} Hemorrhage was considered to be an outcome in four trials,\textsuperscript{63-65,68} mortality in three,\textsuperscript{45,65,68} and rates of splenectomy in
one.46 AE reporting was heterogeneous and generally incomplete. Three trials reported TAEs65,68 or the proportion or number of patients who experienced AEs by treatment.63,68

Study quality
Jadad scores ranged from 1 to 3, and allocation concealment was unclear to adequate. The limitations of internal and external validity of trials appear in Appendix 5 Table 6.

5.4.1 Data analyses and syntheses

a) IVIg versus corticosteroid

Efficacy
The two trials comparing IVIg and corticosteroids included newly diagnosed, untreated adult ITP patients.46,65 Different IVIg dosages and types of corticosteroids were investigated (Appendix 5 Table 6). Patients of European descent were a minority in one46 and likely a majority in the other.65

Jacobs et al., in a trial of 40 participants, found no advantage for IVIg compared with oral prednisone, given that there was no significant difference in improvement in platelet counts, time to peak platelet count, and the proportion of deferred splenectomy (3/13 versus 5/17) over two to three years of follow-up. A proportion of patients in this trial might have had systemic lupus erythematosus (SLE)-associated ITP because positive serology was not an exclusion criterion. No mortality in either treatment group was observed in the preliminary report,45 while the final report did not report mortality data.46

Godeau et al.’s trial was a factorial design comparison between IVIg 0.7 g/kg/day for three days and intravenous methylprednisolone 15 mg/kg/day for three days in which the second randomization (on day four) was to oral prednisone versus placebo.65 The trial on 106 patients was stopped early because of a significant difference in the primary outcome measure between treatment groups in an interim analysis. IVIg had superior efficacy in short-term improvement in thrombocytopenia. Median platelet counts and the proportion of patients with counts greater than 50×10^9/L in the period before second randomization were significantly higher with IVIg treatment. No short-term clinical endpoints were evaluated. Treatment interactions were not statistically significant (Appendix 5 Table 6).

Two meta-analyses were conducted on the proportion of patients with complete remission. This was the only secondary meta-analysis possible. One meta-analysis was based on complete factorial design data, because there was no interaction between treatments. The other was a sensitivity analysis using a subset of non-factorial data to exclude any distortion of treatment effect that could be possible in a factorial design in which treatment interactions were not statistically significant: RR 0.87 (95% CI: 0.38, 1.95) and RR 1.01 (95% CI: 0.25, 4.10) respectively. No significant differences were observed between treatments for this outcome. Statistical heterogeneity (I² more than 50%) was noted in both meta-analyses. This is likely to be attributable to diversity in patient ethnicity; different eligibility or diagnostic criteria (Godeau65 considered positive SLE serology to be an exclusion criterion whereas Jacobs46 did not); and steroid dosage, which was lower in Jacobs et al.’s trial (Appendix 5 Table 6).

Adverse events
Jacobs et al. reported no AE data.46 Therefore, only one trial was available for this assessment.65 Godeau et al.’s trial had a factorial design that observed similar frequencies of AEs between a three-day course of 0.7 g/kg/day IVIg and 15 mg/kg/day methylprednisolone (25% versus 23%).65 Four SAEs associated with the infusion of IVIg resulted in a prolongation of hospitalization. One patient treated with IVIg had a deep venous thrombosis complicated by pulmonary embolus. Other AEs
associated with IVIg were headache (6), fever (5), and headache associated with convulsion in one patient. The AEs associated with corticosteroid were diabetes mellitus (5) and hypertension (2).

**b) IVIg versus anti-D immunoglobulin**

No study was found in this category.

**c) IVIg versus IVIg plus corticosteroids**

**Efficacy and adverse events**

One trial compared IVIg to a combination of IVIg plus corticosteroid in patients with adult untreated ITP.\(^{46}\) In this trial, positive antinuclear antibody was not an exclusion criterion. Thirteen patients were randomized to receive IVIg 0.4 g/kg/day for five days alone or in combination with a tapering dose of oral prednisone 1 mg/kg/day. The duration of steroid therapy was not reported. No harms analysis was undertaken. The rate of initial complete remission was significantly higher with dual therapy (Appendix 5 Table 6).

Over a two- to three-year observation period, the proportion of patients with deferred splenectomy for IVIg versus combination treatment was 3/13 versus 1/13 (p>0.05).

**d) Different doses of IVIg**

Three trials compared different doses of IVIg.\(^{66-68}\) Colovic et al. used a new IVIg preparation that reportedly had higher IgG yield and underwent modified processing.\(^{68}\) Therefore, this trial should be viewed separately from trials involving regular commercially available IVIg.

**Efficacy**

In Colovic’s study,\(^{68}\) no significant difference in efficacy was detected between a two-day infusion of 2 g BT681/kg and a five-day infusion of the identical total dose of BT681. They noted, however, that platelet-related outcomes, including mean (SD) days to platelet count greater than or equal to \(50 \times 10^9/L\) [4.4 (2.8) days versus 2.9 (0.6) days], improved with the five-day regimen, and clinical regression of hemorrhage improved with the two-day regimen. For improvement in platelet counts, one trial suggested that a total dose of 1 g/kg over two days is similar to a total dose of 2 g/kg given over two days. The median (23 days versus 14 days) time to platelet count greater than \(50 \times 10^9/L\) was not significantly different.\(^{66}\) Initial treatment with one IVIg dose of 1 g/kg, however, was more effective than one dose of IVIg 0.5 g/kg.\(^{67}\) Heterogeneity of outcome measures precluded any quantitative data synthesis.

**Adverse events**

In 24 adults with chronic ITP and platelet counts approximately \(20 \times 10^9/L\), Colovic et al. observed that the total and minor AEs were more frequent with a five-day regimen, when compared with a two-day infusion of 2 g BT681/kg. No mortality, SAEs, or WDAEs were observed.\(^{68}\)

In one of two trials, Godeau et al. compared a total IVIg dose of 2 g/kg with 1 g/kg, each over two days (number=20).\(^{66}\) The other investigated a total dose of 1 g/kg with 0.5 g/kg of IVIg, each over one day (number=40).\(^{67}\) Overall, patients had stable chronic thrombocytopenia without major hemorrhage and a platelet count of less than \(50 \times 10^9/L\) (mean count greater than \(20 \times 10^9/L\) for both treatment groups in one trial\(^{65}\) and in one of the two treatment groups in the other) (Appendix 5 Table 6). AEs were not reported by treatment arms except for infusion-related intolerance. This was experienced by one IgA deficient patient in the higher-dose group\(^{66}\) and two patients in the lower-
dose group. Poor AE reporting precluded any comparative safety analysis. Neither trial reported regular AE monitoring.

e) **Regular versus modified IVIg**

**Efficacy and adverse events**

Two phase II double-blind European trials compared five-day 0.4 g/kg/day doses of regular IVIg with identical doses of modified IVIg preparations in adults with chronic ITP and platelet counts less than \(20 \times 10^9/L\). Wolf et al. investigated a modified nano-filtered IVIg preparation to reduce the transmission of bloodborne pathogens (evaluable number=26). Borte et al. analyzed a 12% IgG concentrate with reduced dimer formation and sucrose content (IVIg-F10) (evaluable number=33).

Neither study found any intervention to be superior for platelet-related measures, including mean time to platelet count greater than or equal to \(50 \times 10^9/L\) or regression of bleeding (Appendix 5 Table 6). The trials were too heterogeneous for any quantitative syntheses. In terms of efficacy, the nano-filtered IVIg gave rise to more TAEs than regular IVIg, including one SAE (acute renal failure). IVIg-F10 was associated with two SAEs versus none with regular IVIg. In six months of observation, no viremia was evident in any patient in either study. For both trials, authors concluded or implied that there was comparable efficacy and safety for modified and regular IVIg.

### 5.5 ITP in Mixed Populations

**Trial characteristics**

Two trials fell into this mixed category with sample sizes of 97 and 12 and Jadad scores of 3 and 2 respectively. In one study, data from one subset of patients who received IVIg 0.4 g/kg/day or 1 g/kg/day were used in data analysis.

**5.5.1 Data analysis and syntheses**

a) **Different IVIg preparations**

**Efficacy and adverse events**

In a non-inferiority trial, Bussel et al. examined the safety and efficacy of the same dose (1 g/kg/day for two days) of a new IVIg preparation compared with IVIg-S/D 10% in children and adults with acute or chronic ITP (platelet count less than \(20 \times 10^9/L\)). Non-inferiority was established. We are inclined to interpret this as “equivocal,” given per-protocol analysis with 17% missing data and additional unaccounted non-randomized treatment. Furthermore, a subgroup analysis was lacking. The primary endpoint of the proportion of patients with platelet counts greater than or equal to \(50 \times 10^9/L\) by day 7 was achieved by 90% versus 83% respectively. Approximately 50% of patients in each group experienced at least one AE. Infusions were not premedicated to reduce AEs. Individual drug-related AEs of headache, fever, back pain, and vomiting were similar across both treatments. In all patients, hepatitis A, B, and C; HIV; and parvovirus B19 markers were negative three to six months post-infusion. SAEs were not reported.

One of two trials by Warrier et al. tested higher (1 g/kg for two days) versus lower (0.4 g/kg for two days) IVIg dose in 12 children with an uncertain distribution of acute and chronic disease. Authors defined chronicity as thrombocytopenia for greater than three months. No differences were seen for the primary outcome measure of platelet count greater than \(30 \times 10^9/L\) within 10 days. Both groups had 100% response. Secondary platelet-related outcomes and the number of patients requiring booster and additional doses of IVIg were combined for the two trials. As a result, they were not
considered in this qualitative assessment. Infusion-related AEs were similar across groups (approximately 50%) with each reporting one SAE and aseptic meningitis.50

Given the differences in populations, outcomes, and treatment contrasts, quantitative synthesis was not considered.

6 DISCUSSION

6.1 Summary of Results

Our goals were to determine if IVIg has an incremental benefit over other standard therapy and to identify the role that it should play in the treatment of acute or chronic ITP in children and adults. A total of 28 randomized controlled trials were examined in this clinical review.

6.1.1 Acute ITP in childhood

a) IVIg versus corticosteroids

Eleven trials investigated the efficacy and harms of IVIg versus corticosteroids in acute childhood ITP,44,49,51-54,56-59,61 five of which allowed response-conditional crossover.

Of the six (non-crossover) parallel trials, four showed that IVIg resulted in significantly fewer days with platelet counts less than 30×10^9/L52 or less than 50×10^9/L,54 in higher mean platelet counts in the first week of therapy56 and in a higher proportion of patients with platelet counts greater than or equal to 20×10^9/L at 24 hours and 48 hours.53 Two trials that did not observe any statistically significant result between IVIg and corticosteroid had smaller sample sizes and were conducted in countries with populations of non-European ancestries.51,59

Of the five trials that used response-conditional crossover of patients (partial responders or non-responders or relapsing) to the other treatment group,44,49,57,58,61 response-conditional reassignments are intrinsically different from classic crossover trials in which all randomized patients are switched to the other treatment. This makes conditional crossover reassignments non-randomized, which biases the summary results for the randomized group. Also, carryover and treatment-period effects would be asymmetrically distributed across treatment arms with such study designs. Trial data affected by this bias were excluded from quantitative syntheses, highlighted, and given lesser importance in qualitative syntheses.

Few trials reported data on time to platelet counts greater than or equal to 20×10^9/L and counts greater than or equal to 50×10^9/L.52-54,61 The qualitative syntheses of data for these two outcomes suggest greater IVIg efficacy compared with oral prednisone 2 mg/kg,52 but not higher doses of prednisone or methylprednisolone.53,61 Caution must be exercised, however, in interpreting non-significant results that indicate uncertainty of relative efficacy (or harm) and not equivalency. The equivalency of interventions can be established only through properly conducted trials with predefined upper and lower equivalency margins.70

Quantitative data syntheses of secondary outcome measures indicated that children with acute ITP who had platelet counts less than 20×10^9/L were 55%, 34%, and 17% more likely to achieve counts greater than or equal to 20×10^9/L after 24, 48, and 72 hours of treatment initiation with IVIg
compared with corticosteroids. Sensitivity analyses restricted to higher quality trials with adequate allocation concealment did not change the significance or direction of estimate. The blinding of participants and investigators was not considered to be important, unlike allocation concealment, because the outcome was an objective laboratory measure.

Efficacy data on the clinical outcome of hemorrhage were too sparse for any meaningful interpretation (only five patients in one trial and another reporting zero cases of “serious bleeding” in children without significant baseline hemorrhage).52,56 Two cases of ICH were observed in two trials with a cumulative sample size of 87, in association with corticosteroid therapy only, but ICH was not a specified outcome measure nor systematically investigated to allow even hypothesis generation based on two events.51,58 The available evidence was insufficient to identify subgroups of children who preferentially respond to IVIg. The efficacy of IVIg versus corticosteroid treatment in a subgroup of children with acute ITP in association with parvovirus B19 infection remains unclear, given only one post-hoc analysis on six children. The propensity for progression to chronicity in this subgroup also has not been established. A high probability of type II error is likely, and a larger sample-sized trial is required to address IVIg efficacy in this subgroup.

Overall, the reporting of AE outcomes was poor, precluding any analysis of relative harms. Both treatments induced transient reversible AEs. IVIg was associated with headache, fever, vomiting, and aseptic meningitis in 9% to 30% of patients. Corticosteroids were associated with weight gain, cushingoid features, glycosuria, and behavioural changes in up to 13% of patients. Syntheses of evidence of SAEs were not possible given the rarity of events, selective reporting, and confounding by crossover treatment.

For acute ITP in children, our findings showed that IVIg (0.8 g/kg/day to 1 g/kg/day over one to two days) is more efficacious than corticosteroids in the early improvement of thrombocytopenia to platelet counts greater than or equal to 20×10⁹/L. The relative efficacy of IVIg compared with high doses of methylprednisolone 30 mg/kg remains inconclusive. There is also a consistent lack of a significant difference between IVIg and high dose methylprednisolone across three subgroup meta-analyses in our review — one each for the time points 24 hours, 48 hours, and 72 hours (Table 4).

**b) IVIg versus anti-D immunoglobulin**

Two trials with a total of 208 evaluable patients compared IVIg with anti-D immunoglobulin.53,62 All patients who were administered anti-D immunoglobulin were Rh+, but in one trial some of the included patients who were given IVIg were Rh−. Although it is unclear whether differences in rhesus status could have generated systematic differences in response between the IVIg and anti-D groups, the possibility cannot be excluded.53 Quantitative synthesis of the scant evidence from the two trials is indeterminate for relative efficacy (RR 1.52, 95% CI 0.92 to 2.52 for platelet counts greater than 20×10⁹/L at 24 hours). Indirect qualitative evidence suggested that a total dose of anti-D immunoglobulin less than or equal to 50 μg/kg might be less effective than a total dose of 75 μg/kg.53,62

AE reporting was selective and heterogeneous. Commonly reported drug-related AEs included headache, fever, nausea, and vomiting for IVIg and anti-D immunoglobulin and a reduction in hemoglobin for anti-D immunoglobulin. A nadir of hemoglobin concentration was more likely to occur between one and two weeks with anti-D immunoglobulin. The difference, however, in the reduction of hemoglobin was not statistically significant when IVIg was compared with anti-D.
immunoglobulin.\textsuperscript{53,62} Data on ICH were scant and confounded by prior multiple therapy with corticosteroid, IVIg, and anti-D immunoglobulin.

For this treatment comparison, our relative efficacy and safety findings are inconclusive. They should not, however, be interpreted to imply equivalence, in contrast with two expert opinions.\textsuperscript{32,71} A non-inferiority or equivalence trial is needed to establish equivalence.

c) IVIg versus placebo or expectant management
No trial investigated IVIg versus placebo and only one trial with an evaluable sample size of 35 children compared IVIg with close observation. IVIg was associated with earlier improvements in platelet counts. A reduction in hemorrhage or its incidence was not examined.

Clinical registry data (preliminary prospective “Registry II”) on 407 children with platelet counts less than \(20 \times 10^9/L\) in 41 countries indicate that the overall frequency of severe hemorrhage requiring hospitalization or blood transfusion is 3\% (95\% CI 1.7 to 5.5). The four-week frequency of severe hemorrhage in newly diagnosed ITP patients with no or mild bleeding at presentation was 1.2\% (95\% CI 0.3 to 3.7) when treated and untreated patients were combined. The frequency of severe hemorrhage in untreated newly diagnosed patients with no or mild bleeding at presentation was 1.3\%, suggesting that treatment did not alter the incidence.\textsuperscript{72} A prospective survey in Germany identified 323 children with newly diagnosed ITP.\textsuperscript{73} More than 80\% of them had platelet counts less than \(20 \times 10^9/L\), and more than 50\% had counts less than \(10 \times 10^9/L\). Serious hemorrhage requiring blood transfusion or nasal packing was seen in 2.5\% of patients. No ICH or mortality was observed. These observations warrant trials of acute ITP therapeutic interventions being compared with placebo or no therapy, given the suggested low incidence of serious hemorrhage. Such trials, however, would involve large sample sizes given the rarity of serious bleeding events.

d) Different doses of IVIg
Three trials investigated different doses of IVIg.\textsuperscript{50,53,55} The quality of these trials is poor. Qualitative evidence suggests higher rates of AEs with higher dose IVIg (total 2 g/kg) compared with lower (total 0.6 g/kg to 0.8 g/kg) doses.\textsuperscript{53,55} In combined data, the proportions of children with a platelet count greater than or equal to \(20 \times 10^9/L\) at 48 hours and 72 hours were not statistically significantly different when higher doses were compared with lower doses. No clinical measures of efficacy were assessed. The three trials investigated different IVIg preparations, which might have different dose-response relationships. Thus, the evidence for relative efficacy is inconclusive and suggests that if there is a difference between the two doses, it is small. IVIg in a lower dosage, however, may be safer.

**IVIg in management of acute ITP in children**
IVIg seems to have higher efficacy compared with corticosteroids for early recovery of profound thrombocytopenia in acute childhood ITP, but its superiority over high doses of methylprednisolone is contentious. IVIg and corticosteroids are associated with transient and reversible AEs that are likely to increase in frequency with higher doses.

With the sparse evidence, a therapeutic advantage (incorporating harms and efficacy) of IVIg compared with anti-D immunoglobulin could not be established, but anti-D immunoglobulin was more likely to result in a reduction in patients’ hemoglobin. Therefore, the advantage of IVIg over anti-D immunoglobulin is uncertain.
The optimal dose of IVIg has not been established. Scant evidence indicates that an IVIg dose greater than 1 g/kg may not be better than lower doses of 0.8 g/kg (as one dose). Lower doses, however, might lead to lower AE rates.

Given the limitations in the evidence, IVIg 0.8 g/kg to 1 g/kg as one dose may be given to children with acute ITP with profound thrombocytopenia in preference to corticosteroid. The relative advantage of IVIg over anti-D is uncertain.

There was insufficient evidence to determine if specific subgroups of children with acute ITP may receive preferential benefit from IVIg treatment.

The role of IVIg in chronic childhood ITP could not be established, because evidence from scant, poorly designed, and poorly reported randomized controlled trials could not be synthesized. IVIg was compared with corticosteroids or anti-D immunoglobulin in four randomized controlled trials. The internal validities of the trials were questionable. Response-conditional or optional crossover of refractory patients\textsuperscript{74} or patients with steroid-associated gastrointestinal hemorrhage\textsuperscript{18} and the administration of non-randomized additional treatment to a subset of patients in one treatment arm\textsuperscript{25} confounded the balance established by initial randomization. Therefore, qualitative and quantitative evidence syntheses were not attempted, and estimates of relative safety and efficacy remain indeterminate.

### 6.1.2 Adult ITP

a) **IVIg versus corticosteroids**

The quantitative synthesis of sparse evidence from two trials with a combined sample size of 146 in a selective adult ITP population (those with newly diagnosed untreated ITP) was inconclusive for the efficacy superiority of one treatment over another in terms of short-term complete recovery of thrombocytopenia\textsuperscript{46,65} The synthesis, however, is questionable because statistical heterogeneity between trials was evident, possibly because of differences in population ethnicities and disease inclusion criteria (one of the two studies included lupus-associated thrombocytopenia). A more appropriate qualitative consideration was given to the higher quality trial\textsuperscript{65} which is likely to have examined a patient population largely of European descent with profound ITP and platelet counts of less than 20\times10^9/L. The other trial focused on patients of Xhosa and Malay ethnicities and included those with SLE-associated thrombocytopenia. In this qualitative assessment, treatment with IVIg was associated with significantly more days with platelet counts greater than 20\times10^9/L and 50\times10^9/L in the first three weeks, compared with high dose methylprednisolone, and the difference was significant\textsuperscript{65}.

The evidence for the efficacy of IVIg in the longer term is inconclusive. Both trials failed to detect significant differences in mortality, life threatening hemorrhage, or splenectomy. The frequency of TAEs between IVIg (0.7 g/kg for three days) and high dose methylprednisolone (15 mg/kg for three days) was similar (approximately 20%), but IVIg was associated with more SAEs prolonging hospitalization.

In a systematic literature search, age-adjusted bleeding risk was derived from a pooled analysis of ITP clinical series. The risk of fatal hemorrhage was 0.4%, 1.2%, and 13% per patient-year in age groups younger than 40 years, 40 to 60 years, and older than 60 years respectively. The predicted five-year mortality ranged from 2.2% for patients younger than 40 years to 47.8% for those older than 60 years.\textsuperscript{75}
Evidence from the two randomized trials in this review is lacking for the patients who are at the highest risk of major hemorrhage and mortality (greater than 60 years old). Also, patients in the two trials had acute disease. There is evidence that adults with platelet counts less than $20 \times 10^9/L$ are more likely to follow a chronic course. Furthermore, thrombotic complications of IVIg, although reported in an adolescent, occur more often in older adults.

The Canadian IVIg Hematology Expert Panel recommended no treatment of acute adult ITP when platelet counts are greater than $20 \times 10^9/L$. IVIg should not be used alone as a first line treatment but as part of multi-modality therapy in acute ITP with significant bleeding. IVIg or anti-D are also recommended as second-line adjunctive treatment for acute ITP when an adequate response is not achieved with steroids or as a corticosteroid-sparing adjunctive therapy in chronic ITP post-splenectomy. IVIg was suggested as possible maintenance therapy starting with 0.5 g/kg every four weeks and titrated to the minimum effective dose that can be given at maximum intervals to maintain the platelet count. The scant evidence does not contradict these consensus-based recommendations. It does not, however, support them. The evidence for the role of IVIg in adults with ITP is inconclusive given the lack of clinical outcomes-based trials in the higher risk older population.

b) **IVIg versus anti-D immunoglobulin**

No study was found in this category.

c) **IVIg versus IVIg with corticosteroids**

Limited evidence from the only trial on mainly Xhosa and Malay populations with thrombocytopenia of recent onset, including an association with SLE, with a small sample size of 26 patients, suggests the superior efficacy of dual therapy in effecting initial complete remission of thrombocytopenia. Relative safety was not examined.

Although this trial did not examine patients with platelet counts less than $20 \times 10^9/L$, its evidence is in line with the recommendation of the Canadian IVIg Hematology Expert Panel that acute adult ITP not be treated with IVIg alone, but as part of multi-modality therapy when there is significant bleeding. The benefit of dual therapy over monotherapy was not shown for clinical endpoints.

d) **Higher versus lower-dose IVIg**

Two trials with heterogeneous dosage contrast and platelet-related outcomes examined higher versus lower IVIg doses for efficacy and safety in adults with mostly chronic ITP, with mean platelet counts largely greater than $20 \times 10^9/L$, but all less than $50 \times 10^9/L$. In a qualitative synthesis, scant evidence showed no significant difference in early improved platelet counts when the two IVIg total doses compared were greater than 1 g/kg, unlike comparisons using lower total doses of IVIg. By days 3 and 4 after treatment initiation, however, the single IVIg dose of 1 g/kg was significantly better than 0.5 g/kg in improving thrombocytopenia.

A new IVIg preparation with higher IgG yield (BT681) was also tried in adults with chronic ITP in a total dose of 2 g/kg over two and five days. No significant differences were observed in the improvement of thrombocytopenia, but TAEs were more frequent with a two-day regimen. This qualitative synthesis is consistent with the Canadian IVIg Hematology Expert Panel’s recommendation that in adult symptomatic ITP or one with slow response to steroids, an IVIg dose of 1 g/kg is a reasonable option.
e) **Regular versus modified IVIg**

Two European randomized trials in chronic ITP patients could not establish superior efficacy, based on improvement in platelet counts, of a modified nanofiltered IVIg preparation and a 12% IgG concentrate with reduced dimer formation and sucrose content, in comparison with identical doses of regular, commercially available IVIg.\(^{63,64}\) AE rates were reportedly higher with each modified preparation. Given the heterogeneity, no syntheses were attempted. Equivalency was not established given the absence of prior sample size calculation and predefined upper and lower limits of equivalence for the difference in outcome. The evidence is inconclusive that modified IVIgs are more efficacious than regular IVIg.

### 6.2 Strengths and Weaknesses of This Assessment

This review answered focused questions, using systematic strategies of searching available literature, appraising it, and synthesizing it. Quantitative syntheses, where possible, increased the overall sample size and allowed more robust estimates of the relative efficacy of IVIg compared with other interventions. We considered clinical outcomes and surrogate outcomes in drawing conclusions, avoided the bias introduced by response-conditional crossover of select patients, explored statistical heterogeneity and its explanatory factors, and used the conservative random effects model for quantitative syntheses.

Our conclusions remain far from definitive, largely because of the poor quality of reporting, small sample sizes, the fact that IVIg efficacy was mainly based on surrogate outcome measures with poor predictive value for important clinical events\(^79\) and sparsity of available evidence.

One potential limitation is that the properties of different IVIg preparations were not considered. These may vary in the degree of procoagulant properties such as the impact on propensity for thrombotic complications. There were insufficient data to consider this.

The number of individual trials and the total number of patients evaluated were small. In addition, the methodological quality of the included trials was not high and the follow-up was short.

Because of the small number of trials and missing or insufficient data in the original trials, subgroup analyses could not be performed.

The small number of trials did not allow us to compare pooled IVIg effect estimates in the crossover versus parallel-arm trials. This type of analysis would help to explore the extent of treatment-by-design interaction that may have been present between the two trial designs.

There are other limitations. We assessed English language publications only and included randomized controlled trials but not trials with other study designs. The reporting of harm outcomes in a randomized controlled trial may be insufficient.

### 6.3 Generalizability of Findings

Our findings regarding acute ITP in children showed that IVIg (0.8 g/kg/day to 1 g/kg/day over one to two days) is more efficacious than corticosteroids in the early improvement of thrombocytopenia to platelet counts greater than or equal to 20×10^9/L. The efficacy of IVIg compared with that of high doses of methylprednisolone 30 mg/kg remains inconclusive. There is a consistent lack of a
significant difference between IVIg and high dose methylprednisolone across three subgroup meta-analyses in our review — one each for the time points 24 hours, 48 hours, and 72 hours. These findings, however, are at odds with those in Beck *et al.*’s systematic review. Beck *et al.* found a significant difference in the proportion of patients with platelet counts greater than 20×10⁹/L at 48 hours in favour of IVIg, even when trials were limited to high dose methylprednisolone 30 mg/kg/day. Furthermore, Beck *et al.* showed that IVIg has superior efficacy for the outcome of chronicity. One explanation for this discrepancy could be the fact that they incorporated data from studies that were biased by response-conditional crossover. We restricted the outcome “patients with platelet count less than 150×10⁹/L” in time because the proportion of patients in this category varies with time and because, in most trials, ITP with a longer than six-month duration was considered chronic. The time point of six months, however, does not define chronicity, because 26% to 37% of ITP patients have been reported to undergo complete remission between six and 12 months, with an additional 50% recovering in one to two years without splenectomy or immunosuppressive therapy. As a result, a 12-month time point for designating chronicity has been proposed. It is possible then that our six-month endpoint of a platelet count less than 150×10⁹/L captured a mix of acute and chronic childhood ITP.

There is insufficient evidence to draw conclusions about the clinical efficacy of IVIg in ITP, and the link between the early recovery of platelet count and the reduction in morbidity and mortality due to bleeding remains uncertain. For the treatment of patients with active bleeding, evidence from retrospective and prospective studies indicates that patients respond poorly in terms of improvement in platelet counts. Few trials enrolled patients with active hemorrhage. There is no direct evidence establishing positive and negative predictive values of platelet count as a predictor of clinically important and severe hemorrhage. Given the observation, however, that most (more than 80%) children experiencing life threatening or transfusion-requiring hemorrhage have a platelet count less than 20×10⁹/L, the sensitivity of this cut-off platelet count is likely to be high (the ability to “rule out” those at highest risk of major bleed). In contrast, observations that no more than 3% of patients with platelet counts less than 20×10⁹/L actually experience serious hemorrhage indicate low specificity of the same cut-off (poor ability to “rule in” those likely to experience major bleed). This would make the platelet count a poor surrogate marker of hemorrhagic risk in ITP patients or one with low predictive value. Nevertheless, improvement in platelet count above 20×10⁹/L is the best available primary outcome measure in the literature. A review of 56 published cases of ICH in children with ITP indicated that 98% had platelet counts less than 20×10⁹/L at the time of hemorrhage, while 73% had counts below 10×10⁹/L. Furthermore, childhood ITP-associated ICH is a serious event associated with up to 50% mortality. Therefore, the hematologic efficacy of interventions to raise counts above 20×10⁹/L can be interpreted for clinical efficacy in the absence of true measures.

### 6.4 Knowledge Gaps

Research is still needed to answer some clinical questions:

- Is IVIg safer and more efficacious than anti-D immunoglobulin in Rh+ patients?
- Is lower-dose IVIg safer and equally efficacious as higher-dose IVIg in children?
- What benefit does dual or multi-modal treatment offer to children with acute ITP at high risk of major bleeding?
- Can we predict which children with ITP and profound thrombocytopenia are at highest risk for serious hemorrhage or progression to chronic ITP?
• How does IVIg compare with placebo or expectant management with respect to serious hemorrhage in children?
• How does IVIg compare with placebo or expectant management with respect to chronicity in children with acute ITP?
• Can we predict which children with acute ITP will preferentially respond to IVIg? Is IVIg more efficacious than corticosteroid treatment in children with acute ITP associated with parvovirus B19 infection? What are their effects on chronicity, given the unconfirmed findings presented in this review?
• How does IVIg compare with other treatment including expectant management in adults, particularly the elderly who may be at increased risk of serious hemorrhage and thrombotic complications of treatment?

7 CONCLUSIONS

7.1 Acute ITP in Children

A qualitative synthesis suggests that IVIg resulted in significantly fewer days with platelet counts less than 50×10^9/L than oral prednisolone 2 mg/kg (median of two versus four days), but discrepant results were observed when IVIg was compared with prednisolone 4 mg/kg/day or methylprednisolone 30 mg/kg/day.

Our quantitative synthesis shows significant differences in the proportion of patients with platelet counts equal to or greater than 20×10^9/L, in favour of IVIg compared with corticosteroids.

The role of IVIg in chronic childhood ITP could not be established because evidence from scant, poorly designed, and poorly reported randomized controlled trials could not be synthesized.

7.2 Adult ITP

Sparse evidence indicates that in adults with profound thrombocytopenia, IVIg may be more efficacious than high dose corticosteroids in improving platelet counts in the short term than high-dose corticosteroids, but possibly at the risk of more SAEs. The effect of IVIg on clinical outcomes remains indeterminate. An initial randomized controlled trial report suggests better short-term platelet response with IVIg and corticosteroid dual therapy. Evidence from randomized controlled trials was unavailable for the comparison of IVIg and anti-D immunoglobulin. Limited evidence in adults with chronic ITP but without severe hemorrhage could not demonstrate the superiority of a 2 g/kg dose of IVIg over a 1 g/kg dose. An IVIg dose of 1 g/kg, however, may be better than a dose of 0.5 g/kg. There were no randomized controlled trials on pregnancy-associated ITP.

In conclusion, there are insufficient data to determine whether IVIg has an advantage over other interventions in the long-term management of adult ITP. It is also unclear whether the superiority of IVIg in improving platelet counts will translate into better clinical benefit in the acute management of the elderly population who are at highest risk of hemorrhage, because the one clinical trial showing better the hematologic efficacy of IVIg compared with corticosteroid was conducted on newly diagnosed ITP patients, mostly younger than 60 years old. IVIg in combination with corticosteroid
seems to be promising in the management of acute ITP in adults, but trials are needed to investigate clinical endpoints in the population most at risk.

8 REFERENCES


APPENDICES

Available from CADTH’s web site
www.cadth.ca