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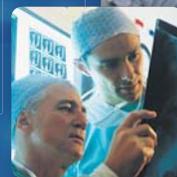
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Intravenous Immunoglobulin for Treatment of Idiopathic Thrombocytopenic Purpura: Economic and Health Service Impact Analyses



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Canadian Agency for Drugs and Technologies in Health

**Intravenous Immunoglobulin for Treatment
of Idiopathic Thrombocytopenic Purpura:
Economic and Health Service Impact Analyses**

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September 2008

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Industry: The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Talecris Biotherapeutics and Baxter Canada. Comments were received from all manufacturers and were considered when preparing the final report.

Authorship

Gord Blackhouse was the lead author for the review of economic studies, one of the primary economic analyses [childhood idiopathic thrombocytopenic purpura (ITP)], and the budget impact analysis. He acted as the project lead. He reviewed drafts and provided approval of the final version.

Feng Xie was the lead author for one of the primary economic analyses (adult ITP), the background section of the report, and the study protocol. He designed the economic model and conducted the economic evaluation, reviewed drafts, and provided approval of the final version.

Kaitryn Campbell was responsible for the design and execution (performance) of the literature search strategies, the associated appendix, and the bibliographies. She was the lead author for the ethical review write-up. She reviewed drafts and provided approval of the final version.

Nazila Assasi helped design the search strategy for the ethical review, reviewed studies, and abstracted data for the ethical review. She reviewed drafts and provided approval of the final version.

Kathy Gaebel helped write the Introduction section of the report, interpreted clinical data, and helped address internal and external reviewer comments. She reviewed drafts and provided approval of the final version.

David Pi participated in the development of the protocol. He provided answers to clinical related questions during the course of the project and participated in the development of the economic analyses. He reviewed drafts and provided approval of the final version.

Mitch Levine participated in the development of the economic analyses. He also provided answers to clinical questions during the course of the project. He reviewed drafts and provided approval of the final version.

Mita Giacomini reviewed and provided advice on several iterations of the ethical write up of the report. She reviewed drafts and provided approval of the final version.

Ron Goeree participated in the development of the protocol and in the development of the economic analyses. He provided overall direction for the project. He reviewed drafts and provided approval of the final version.

Raymond Banks peer reviewed the search strategy, verified the draft report for references, and provided approval of the final version.

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Conflicts of Interest

Feng Xie, Kaitryn Campbell, Nazila Assasi, David Pi, Mita Giacomini, and Raymond Banks disclosed no conflicts of interest. Gord Blackhouse received funding from Eli Lilly Canada Inc. and GlaxoSmithKline Inc. for consulting. Mitch Levine received funding from AstraZeneca Canada Inc., Eli Lilly Canada Inc., Pfizer Canada Inc., and Merck Frosst Canada Inc. and acted

as expert witness for Novartis Pharmaceuticals Canada Inc. and Wyeth Canada. He was also Chair, Expert Drug Committee for Health Canada. Kathy Gaebel received funding grants from Abbot Laboratories Limited and Amgen Inc. for consulting and travel. Ron Goeree was an advisory board member to Janssen-Ortho Inc. and Hoffman-La Roche Ltd., and a consultant for Eli Lilly Canada Inc. The drugs were unrelated to the treatment of ITP.

Intravenous Immunoglobulin for Treatment of Idiopathic Thrombocytopenic Purpura: Economic and Health Service Impact Analyses

Technology

Intravenous immunoglobulin (IVIg), a blood product containing pooled IgG immunoglobulins derived from human plasma.

Condition

Idiopathic thrombocytopenic purpura (ITP) caused by an abnormal immune response that leads to low platelet counts and bleeding.

Issue

Because of the growing use of IVIg in Canada (including off-label use), escalating costs, potential availability of other treatments, and uncertainty about therapeutic advantages, there is a need to assess the cost-effectiveness of IVIg in the treatment of ITP.

Methods and Results

A systematic review was conducted to identify economic evaluations that compared IVIg with alternative treatments. Four evaluations were included. Relevant clinical studies were identified. Two primary cost utility analyses were conducted.

Implications for Decision Making

- **The cost-effectiveness of IVIg is more favourable in acute childhood ITP than in chronic adult ITP.** In acute childhood ITP, when IVIg was compared with prednisone, anti-D, methylprednisolone, or observation, IVIg was the most costly option and resulted in the largest number of lifetime quality-adjusted life years (QALYs). IVIg has the highest probability of being cost-effective if decision makers are willing to pay more than \$112,000 per QALY. These results are sensitive to the probability of intracranial hemorrhage, the IVIg dose, and the patient's weight. In chronic adult ITP, compared with prednisone, IVIg is cost-effective if decision makers are willing to pay \$2,690,000 per QALY.
- **The health services impact depends on the patient population.** Based on the use of foreign prevalence and incidence data to derive Canadian estimates, there are 6,090 chronic adult ITP cases compared with 268 acute childhood ITP cases. The annual per-patient maintenance costs are \$26,931 for chronic adult ITP versus \$1,598 for acute childhood ITP.
- **Some uncertainty remains.** These analyses are based on data from international sources. There is a need for Canadian patient-level health resource utilization and utility data from randomized controlled trials that compare IVIg with alternative therapies.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Blackhouse G, Xie F, Campbell K, Assasi N, Gaebel K, Levine M, Pi D, Giacomini M, Goeree R, Banks R. *Intravenous Immunoglobulin for Treatment of Idiopathic Thrombocytopenic Purpura: Economic and Health Service Impact Analyses*.

EXECUTIVE SUMMARY

The Issue

Intravenous immunoglobulin (IVIg) is a blood product that 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 rates of per capita users of IVIg as does the US. The average yearly increase in IVIg use reported by Canadian Blood Services from 1997 to 2008 is 11.3%, with a range of 6.8% to 20.0%.

There are a few approved indications for IVIg use and a growing number of off-label uses. IVIg treatment for patients with neurological and hematological disorders accounted for 50% of all IVIg use in four Toronto hospitals from 1995 to 2000. Bone marrow transplant recipients and patients with infectious diseases consumed an additional 28%. The escalating cost, an increasing demand, a growing number of indications, and an IVIg shortage have prompted Canada to adopt new approaches to manage IVIg use in terms of costs and effects.

Idiopathic thrombocytopenic purpura (ITP) is one of the most common hematological disorders. It is the result of an abnormal immune response to disease-related or indeterminate antigens. ITP is characterized by accelerated immune-mediated destruction of autoantibody-coated platelets, causing thrombocytopenia (platelet count of less than 150,000/ μ L) and subsequent mucocutaneous bleeding. Assessing the costs and effectiveness of IVIg use in patients with ITP is a priority, given the high utilization rates in Canada, the potential availability of alternative treatments, and an uncertainty about the therapeutic advantage over alternative therapies.

Objectives

This study investigates the cost-effectiveness and health service impact of IVIg for the treatment of ITP in Canada by answering the following research questions:

- What is the economic evidence regarding the cost-effectiveness of IVIg for ITP?
- What is the cost-effectiveness of the use of IVIg for pediatric patients with ITP in Canada?
- What is the cost-effectiveness of the use of IVIg for adult patients with ITP in Canada?
- What is the impact on health services of IVIg use (including an estimated population impact, budget impact, and impact on legal, ethical, and equity issues) as a treatment for ITP in Canada?

Methods

A systematic review was conducted to identify published economic evaluations that compared IVIg to alternative therapies for ITP. The search strategy was developed by an information specialist (KC) with input from the project team. It underwent peer review by a CADTH information specialist. Based on the identified published economic evaluations and input from clinical experts, two primary economic evaluations were conducted. One model compared treatments for acute ITP (IVIg, anti-D, prednisone, methylprednisolone, observation), and the other model compared treatments (IVIg, prednisone) for chronic adult ITP. A published CADTH systematic review of IVIg for the treatment of ITP was used to identify relevant clinical studies. Additional literature searches were conducted to identify the information needed to estimate the population and budget impacts of IVIg. The current and potential future budgetary impacts of IVIg for the treatment of ITP were estimated. Finally, the clinical and economic papers that were

selected were reviewed for discussions on ethical, psychosocial, legal, and implementation issues. A summary of these issues was written.

Results

In the economic evaluation of acute childhood ITP, the use of IVIg compared with single-dose anti-D was associated with an additional 0.0025 QALYs (from 17.6933 to 17.6958) and an additional \$140 (from \$1,940 to \$2,080) per patient, resulting in an incremental cost-effectiveness ratio of \$56,000 per QALY. In the base case analysis, it was assumed that there was one IVIg dose of 0.8 g/kg and that the patient weighed 20 kg. Among the alternatives compared (IVIg, anti-D, prednisone, methylprednisolone, observation), IVIg was the most costly and it resulted in the largest number of lifetime QALYs. Compared with the alternatives, IVIg has the highest probability of being cost-effective if society is willing to pay more than \$112,000 for a QALY. The cost-effectiveness results were sensitive to several assumptions, including the probability of intracranial hemorrhage on each day that the children had platelet counts of less than 20,000/ μ L, the dosing regimen of IVIg, and the weight of the patient.

In the chronic adult economic model, the use of IVIg compared with prednisone was associated with an additional 0.003 QALYs (from 11.9385 to 11.9415) and an additional \$8,070 (from \$10,430 to \$18,500) per patient, resulting in an incremental cost-effectiveness of more than \$2 million per QALY. The clinical literature showed that IVIg and prednisone had similar rates of treatment response (0.76 versus 0.74) and relapse (0.52 versus 0.49), leading to the small long-term difference in QALYs. The findings from our review of the economic data and from primary modelling suggest that compared with prednisone, IVIg is unlikely to be a cost-effective treatment for adults with chronic ITP, unless decision-makers are willing to pay more than \$500,000 for a QALY.

The current annual budgetary cost of IVIg treatment for ITP in Canada was estimated to be \$34.5 million. The potential annual budgetary cost if all ITP patients were treated with IVIg was estimated to be \$192 million. Ethical, psychosocial, and legal issues regarding IVIg treatment include side effects, standardization of use, supply limitations, and the danger of disease transmission through blood products.

Conclusions

The two primary economic evaluations that were conducted in this review indicate that the cost-effectiveness of IVIg for the treatment of ITP may differ according to the patient population. The cost-effectiveness of IVIg was found to be more favourable in the childhood ITP population than in the chronic ITP adult population.

The differences between the two cost-effectiveness model results should be considered given the potential impact of IVIg on health services in Canada. Based on published prevalence and incidence studies, the number of chronic adult cases of ITP and the associated maintenance costs were estimated to be larger than the number of acute childhood cases and the associated costs.

The economic evaluations in the analysis are based on models that synthesize data from various sources. A possible next step that would help answer our research questions would be to conduct Canadian randomized trials that include the collection of patient level health resource utilization and utility data and compare the IVIg treatment options.

ABBREVIATIONS

CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CINAHL	Cumulative Index to Nursing and Allied Health Literature
HEED	Health Economic Evaluations Database
ICER	incremental cost-effectiveness ratio
ICH	intracranial hemorrhage
ICUR	incremental cost utility ratio
ITP	idiopathic thrombocytopenic purpura
IVIg	intravenous immunoglobulin
NHSEED	National Health Services Economic Evaluation database
NIS	Nationwide Inpatient Sample
QALD	quality-adjusted life day
QALY	quality-adjusted life year

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- APPENDIX 7: Graphical representation of Adult ITP model
- APPENDIX 8: IVIg Planning, Implementation, Utilization, Legal, Regulatory, Ethical and Psychosocial Issues Abstraction Form

1 INTRODUCTION

1.1 Background

1.1.1 Disease

Idiopathic thrombocytopenic purpura (ITP) is one of the most common hematological disorders.¹ The incidence of ITP has been estimated to be 4.8 per 100,000 in children² and 2.6 per 100,000 in adults.³ The median age of children presenting with ITP, identified from cohort studies, is reported to be between 5 and 6 years.⁴⁻⁶ ITP can be manifested in neonates who are born to mothers with ITP.⁴ The youngest individual in the cohort studies was one month old. Prevalence estimates for the 0 to 4 years of age group are 8.37 for females and 9.09 for males.⁷ The estimates increase for the 5 to 17 years of age group (12.6 and 9.30 for females and males respectively). Adult ITP occurs most commonly between 18 and 40 years of age.¹ The prevalence estimates for adult ITP increase with age. The highest prevalence estimates are for the 65+ age category (35.8 and 38.3 for females and males respectively).⁷

The natural history of ITP differs in children and adults. Children who were previously healthy usually present with a short history of mucocutaneous bleeding (for example, bruising and petechiae) over a few days to weeks after an infectious viral illness and with a low platelet count (less than 20,000/ μ L). The disease usually resolves itself without treatment with a favourable prognosis in more than 70% to 90% of cases within six months,^{1,4} while 10% to 20% of children may develop a chronic form for which there is limited published evidence on the evaluation of effective treatment options. Intracranial hemorrhage (ICH) is the most serious life-threatening complication that is most likely to occur when the platelet count is less than 20,000/ μ L.⁸ The risk of ICH is estimated to be between 0.1% and 1% and occurs most often during the first 48 hours of onset.⁸ The main goal of treatment for acute childhood ITP is the prevention of serious and potentially fatal bleeding. There is debate about the optimal management approaches. The options include close observation without treatment, corticosteroid therapy,⁹ and splenectomy.¹⁰

Blood products that are isolated from large volumes of human plasma by cold-ethanol fractionation include polyclonal intravenous immunoglobulin (IVIg)⁹ and anti-D immune globulin [in Rhesus (Rh) positive non-splenectomized children].¹¹ IVIg contains all five mammalian antibody isotypes (IgA, IgD, IgE, IgG, IgM), but IgG is the major component. Anti-D immunoglobulin contains only the isotype IgD. Because it targets the D antigen, it will be effective only in persons who carry this antigen on their blood cells known as Rh positive blood type.

Most children are managed on an outpatient basis, especially if there is no bleeding. Hospitalization and emergency treatment are appropriate for those with platelet counts of less than 20,000/ μ L and life-threatening bleeding, those with mucous membrane bleeding, or those who are inaccessible or non-compliant.^{12,13} An expert panel of hematologists has described the treatment of ITP with recommended dosing regimens, including an example of the medical management of an adult with ITP (Appendix 1).¹³

ITP in adults often has a more persistent course.¹ It may last for years and is characterized by recurrent relapses that often require medical intervention. Treatment options for adults with chronic ITP include corticosteroids, IVIg, and anti-D immune globulin. Splenectomy is generally recommended within three to six months if a relapse occurs or if the disease is refractory to the treatments that have been mentioned. Approximately 5% of adults with ITP have chronic refractory ITP, which is defined as the failure of any modality to maintain a platelet count above 20,000/ μ L.¹⁴ Chronic refractory ITP is associated with an increase in mortality.¹⁵

1.1.2 Technology

IVIg is a blood product containing pooled IgG immunoglobulins. It is used as a replacement therapy in primary and secondary humoral immunodeficiencies and as an immunomodulatory therapy in autoimmune diseases and transplantation.^{16,17} No single mechanism accounts for all the immunomodulatory effects of IVIg. The blockage of the Fc receptor on macrophages of the reticuloendothelial system accounts for the immediate effects of IVIg. The blockage comes from a competitive interaction of IVIg with anti-platelet antibodies for the Fc receptor and from the competition of soluble Fc γ receptors with membrane Fc receptors for circulating IVIg-sensitive platelets.¹⁸ The long-term effect of IVIg can be attributed to the immunomodulatory effects of IVIg on T cells and macrophages. IVIg enhances T cell suppressor function and inhibits B cell function or antigen-processing cells via the Fc receptor.¹⁸

The most common adverse events of IVIg, which are related to the speed of infusion, occur in 10% to 18% of infusions. These events include fever, chills, and facial flush; tachycardia, palpitations, chest tightness, or chest pain; dyspnea; back pain, joint pain, myalgia; and hypotension and shock. They are all reported to be mild and reversible. Slowing the speed of infusion usually prevents their reoccurrence.¹⁹ Anaphylactic or anaphylactoid reactions to the IgA component of IVIg are rare.

Renal events have been reported with high-dose IVIg (1 mg/kg to 2 mg/kg). These events occurred in patients with pre-existing disease (renal disease, diabetes) and are associated with the use of sucrose as a stabilizing sugar during fractionation. The use of sugar has been eliminated in new preparations.¹⁹ Aseptic meningitis has been reported with high-dose IVIg in patients with autoimmune neuromuscular disease. Migraines have been identified as the predisposing factor.

Cardiovascular events range from cardiac ischemia and myocardial infarction to thromboembolic events (deep vein thrombosis, central retinal vein occlusion, pulmonary embolism, stroke). Contributing risk factors for these events were related to the patient's cardiovascular system and hydration status.¹⁹ Unusual reactions reported with IVIg therapy are progressive neurodegeneration in patients with immune deficiency, serum sickness, hemolytic reactions due to isoagglutinins (antibodies in the serum) to Rh or other blood groups, neutropenia, transfusion-related acute lung injury, alopecia, uveitis, and dermatological events.

IVIg is available as four products through Canadian Blood Services (Table 1).

Table 1: IVIg products available through Canadian Blood Services

Brand Name	Manufacturer	Sizes Available
Gammagard-SD [®]	Baxter Bioscience	2.5 g, 5.0 g, 10.0 g
Gamunex [™] , 10%	Talecris Biotherapeutics	2.5 g, 5.0 g, 10.0 g, 20.0 g
IGIVnex [™] , 10%	Talecris Biotherapeutics / Canadian Blood Services	10.0 g, 20.0 g
Iveegam [®] EN	Baxter Bioscience	5.0 g

IVIg=intravenous immunoglobulin.

Canada's plasma supply comes from voluntary donations in Canada and from paid donors in the US.¹² Canada is one of the highest per capita users of IVIg, as is the US.²⁰ The average yearly increase in IVIg use reported by Canadian Blood services from 1997 to 2008 is 11.3% , with a range of 6.8% to 20.0%.²¹ The cost of IVIg is \$550 to \$1,100 per infusion of 0.5 g/kg to 1.0 g/kg for a 20-kg child and \$4,000 per infusion of 1 g/kg for a 70 kg adult.¹²

ITP, a licensed indication for IVIg, accounted for the highest usage in the adult population. ITP also accounted for the highest total usage in the pediatric population across Canada.²²

2 THE ISSUE

Canada has one of the highest rates of per capita users of IVIg along with the US. The average yearly increase in IVIg utilization reported by Canadian Blood Services from 1997 to 2008 is 11.3%, varying from 6.8% to 20.0%.

There are a few approved indications for IVIg and a growing number of off-label uses. IVIg treatment for patients with neurological and hematological disorders accounted for 50% of all IVIg use in four Toronto hospitals from 1995 to 2000. Bone marrow transplant recipients and patients with infectious diseases consumed an additional 28%.²² Escalating cost, increasing demand for an expanding number of indications, and an IVIg shortage have prompted Canada to adopt new approaches to manage IVIg use.

ITP is one of the most common hematological disorders. It is the result of an abnormal immune response to disease-related or indeterminate antigens and is characterized by accelerated immune-mediated destruction of autoantibody-coated platelets, causing thrombocytopenia (platelet count of less than 150,000/ μ L) and subsequent mucocutaneous bleeding. Assessing the costs and effectiveness of IVIg use in patients with ITP is a priority, given the high utilization rates in Canada, the potential availability of alternative treatments, and the uncertainty of a therapeutic advantage over alternative therapies.

3 RESEARCH QUESTIONS

The study focuses on the following four research questions:

- What is the economic evidence regarding the cost-effectiveness of IVIg for ITP?

- What is the cost-effectiveness of the use of IVIg for pediatric patients with ITP in Canada?
- What is the cost-effectiveness of the use of IVIg for adult patients with ITP in Canada?
- What is the impact of IVIg on health services (including an estimated population impact, budget impact, and impact on legal, ethical, and equity issues) when it is used as a treatment for ITP in Canada?

4 ECONOMIC ANALYSIS: REVIEW OF EXISTING LITERATURE

4.1 Methods

4.1.1 Literature Search

A systematic search was undertaken to locate full economic evaluations assessing IVIg for ITP or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The original intent of the project was to review IVIg studies for ITP or CIDP. The scope of the project was subsequently changed to include only studies for ITP. The initial search results and title or abstract screening results include ITP and CIDP studies. The search strategy was developed by an information specialist (KC) with input from the project team. The strategy underwent peer review by a CADTH information specialist. All search results were imported into a Reference Manager Version 11 database to eliminate duplicates and for title or abstract screening.

The following bibliographic databases were searched through the Ovid interface: MEDLINE (1950 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to present). Parallel searches were run in PubMed (for non-MEDLINE records only), Wiley’s Cochrane Library (NHS Economic Evaluation Database and Health Technology Assessment Database) and Health Economic Evaluations Database (HEED), Thomson’s Social Sciences Citation Index and BIOSIS Previews, and Scholar’s Portal’s EconLit.

The search strategy with controlled vocabulary and keywords focused on the concepts of “ITP” or “CIDP” and “IVIg.”

An unvalidated methodological filter was applied to limit retrieval to primary economic studies or reviews of economic studies. No year or language limits were used (Appendix 2).

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies as well as health economic research groups and their associated databases. Google and AlltheWeb search engines were used to search for additional information. These searches were supplemented by reviewing the bibliographies and abstracts of key papers and conference proceedings.

Ovid and PubMed AutoAlerts were set up to send monthly updates with any new literature. Monthly updates were performed on the HEED and NHSEED databases.

4.1.2 Study Selection

Study selection was done in two phases: title or abstract review and full text review. Two independent reviewers (GB, FX) conducted the title and abstract review, using prespecified inclusion and exclusion criteria. Based on the titles and abstracts (when available), studies were excluded if both reviewers agreed that an economic evaluation was not included, that IVIg was not included as a comparator, or that the patient population did not include those with ITP. Studies that were not excluded based on title and abstract screening were retrieved in full text and assessed by one reviewer (GB) to determine if they should be included for data abstraction. Inclusion criteria for full text screening were analysis of ITP in the study, inclusion of IVIg as a treatment comparator, measurement of costs, and measurement of effectiveness.

4.1.3 Data Abstraction

One reviewer (GB) abstracted data from the economic evaluations using standard forms created for this project (Appendix 3). A second reviewer (FX) verified the data.

4.1.4 Results of Literature Search

Of the 293 potentially relevant economic evaluation reports that were identified through the literature review (Figure 1), 23 articles were retrieved for full text screening. Nineteen of these articles were excluded (Appendix 4). This resulted in four relevant economic evaluation studies for review.

4.2 Results of Economic Review

Four economic evaluations of IVIg for the treatment of ITP were reviewed. One study compared IVIg with splenectomy in children with chronic ITP.²³ The other three studies compared IVIg with alternative treatments (prednisone, prednisolone, anti-D) in children with acute ITP.²⁴⁻²⁶ No economic evaluations evaluating IVIg treatment for ITP in adults were identified. Table 2 provides a comparative summary of the economic analyses from the four studies.

4.2.1 Kumar et al., 2005

In a retrospective chart review, Kumar et al.²⁴ estimated the costs and outcomes of consecutive children (aged 18 years or younger) who were treated for ITP at a US health care institution between 1997 and 2001. Patients were classified by initial ITP treatment: IVIg (n=60), anti-D (n=60), steroids (n=42), and observation (n=27). The clinical outcomes that were analyzed included the number of days until the platelet count was greater than 20,000/ μ L, the proportion of patients with platelet counts greater than 20,000/ μ L by Day 7, the proportion needing re-treatment, and the proportion with side effects.

Patient costs, in US dollars, were based on actual physician billing and hospital charges for each patient encounter. The year of the costs depended on the year of the patient encounter, and no common year was specified. Clinical outcomes were recorded from patient charts.

Figure 1: QUORUM flowchart

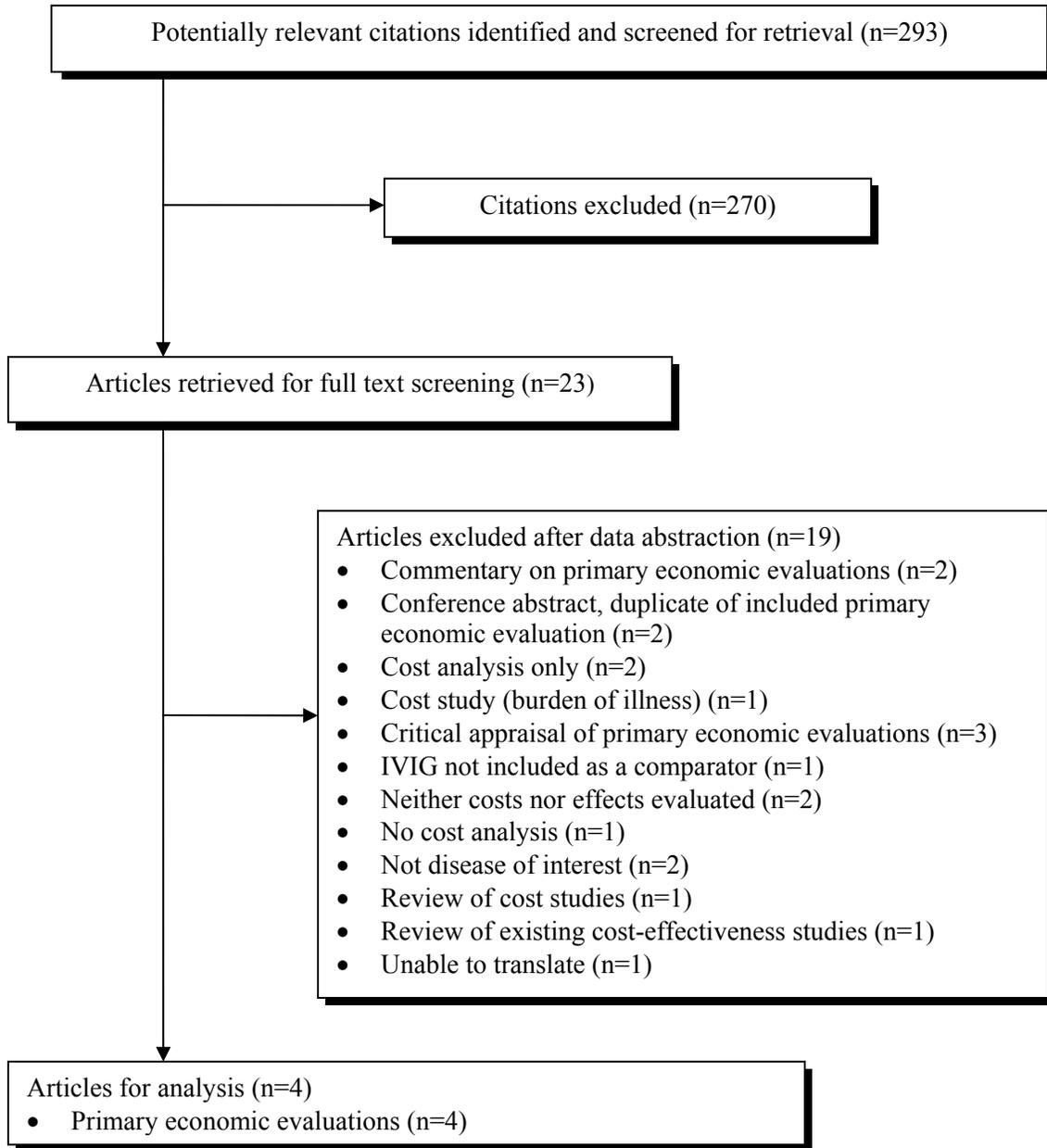


Table 2: Economic evaluations of ITP

	Hollenberg et al., 1988	Kumar et al., 2005	O'Brien et al., 2007	Adams et al., 2001
Patient population	Children 10 years of age and 35 kg with chronic ITP	Children <18 years with ITP	Children with acute ITP and platelet count <20,000, weight of 20 kg, 5.7 years of age	Patients 1 to 15 years of age with primary diagnosis of ITP or treated for ITP related sequelae
Comparators	Splenectomy, IVIg	Anti-D, IVIg, steroids, observation	IVIg, anti-D, IV methylprednisolone, prednisone	Anti-D 50 µg/kg, IVIg 0.8 g/kg, IVIg 1 g/kg
Type of analysis	10-year Markov model	Patient level analysis	Short term decision model	Patient level analysis
Sources of clinical data	Published literature, (no systematic review), unpublished survey, expert opinion	Retrospective chart review of acute ITP patients seen at an Indiana hospital	Literature review	Administrative database
Sources of cost data	“Actual charges and present reimbursement rates in New York City.” Unit cost of IVIg based on “wholesale price.” Costs in 1986 US\$	Based on actual physician bills and hospital charges for each patient encounter, US\$	2004 Red Book average wholesale prices, local hospital Medicare reimbursement data, 2004 US\$	Average wholesale prices, Medicare physician fees, US\$
Cost-effectiveness outcome	\$ per death avoided	\$ per day platelets <20,000/µL avoided	\$/QALD	\$/life year saved
Incremental cost-effectiveness or cost utility	IVIg \$540,130 per death avoided versus splenectomy	Steroids reference strategy anti-D \$150 per day with platelet counts <20,000/µL avoided versus steroids IVIg \$889 per day with platelet counts <20,000/µL avoided versus anti-D	IVIg and methylprednisolone dominated. Anti D \$7,616/QALD compared with prednisone, equivalent to \$2.8 million/QALY	Average ratios presented IVIg 0.8 g/kg \$4,792 per life year gained Anti-D \$4,892 per life year gained
Sensitivity analyses	Changing proportion of patients curable by IVIg ±25% varied ICER from \$166,000/death avoided to \$1,200,000/death avoided. Changing cost of IVIg from \$35/g to \$21/g made	None	Sensitivity analyses conducted around all model variables. Lowest cost per QALD for anti-D compared with oral prednisolone was \$1,678, equivalent of \$612,000 per QALY	None

Table 2: Economic evaluations of ITP				
	Hollenberg et al., 1988	Kumar et al., 2005	O'Brien et al., 2007	Adams et al., 2001
	IVIg dominant. If children ≤ 6 years old, IVIg becomes dominant			
Authors' Conclusions	No conclusion on base-case cost-effectiveness. "Initial IVIG treatment of younger children with chronic ITP is clearly a cost-effective strategy"	No conclusions on cost-effectiveness	Cost per QALY of anti-D far exceeds "the often quoted values of \$50,000/QALY to \$100,000/QALY"	Cost per life year saved estimates "are well within the range of socially cost-effective therapies"

ICER=incremental cost-effectiveness ratio; ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin; QALD=quality-adjusted life day; QALY=quality-adjusted life year.

The authors did not assess cost-effectiveness. Based on the initial treatment costs and the outcomes that were presented, however, comparative cost-effectiveness can be estimated. Patients who were only under observation were excluded from the analysis because their median platelet count at baseline was 47,000/ μ L. The median costs of patients treated with steroids, anti-D, and IVIg were \$1,737, \$2,037, and \$2,926 respectively. The median numbers of days with platelets less than 20,000/ μ L were six for steroid-treated patients, four for anti-D-treated patients, and three for IVIg-treated patients. The incremental cost-effectiveness of moving from steroids to anti-D can be estimated as \$150 per day with a platelet count of less than 20,000/ μ L avoided. The incremental cost-effectiveness of moving from anti-D to IVIg can be estimated to be \$889 per day with a platelet count of less than 20,000/ μ L avoided.

The authors did not formally evaluate cost-effectiveness, so conclusions about relative cost-effectiveness could not be calculated.

4.2.2 O'Brien et al., 2007

Using a decision analytic model, O'Brien et al.²⁵ conducted an economic evaluation of treatment options for acute childhood ITP. The starting cohort of the model was children with acute ITP, a platelet count of less than 20,000/ μ L, and a weight of 20 kg. The treatment options that were evaluated included IVIg (single dose 0.8 g/kg), anti-D (single dose 75 mg/kg), intravenous methylprednisolone 30 mg/kg dose over three days, and oral prednisone 4 mg/kg/day for four days.

In the model, it was assumed that all patients were hospitalized and then discharged once their platelet count reached 20,000/ μ L. Patients were at risk of developing treatment side effects and ICH during their hospitalization. The probability of side effects varied between treatment strategies. Costs and utility decrements were applied to side effects, to ICH, and to each day that patients were hospitalized.

The primary economic outcome was the incremental cost per quality-adjusted life days (QALDs). The analysis was taken from a societal perspective. Therefore, it included the costs

that were related to medications, blood products, treatment infusion, side effects, number of days in hospital, ICH, and the time parents took off work. The time horizon of the model was the duration of the acute hospital admission. Costs were in 2004 US dollars. Medication costs were based on the average 2004 Red Book wholesale prices. The cost for days off work was based on average hourly US wage rates. Other costs were based on the authors' institutions' finance departments.

The main clinical efficacy data that drove the model were the number of days to reach platelet counts of greater than $>20,000/\mu\text{L}$ and the probability of side effects associated with each treatment. The authors stated that a literature search was conducted to estimate the time to reach platelet counts greater than $20,000/\mu\text{L}$ and the probability of side effects. The estimated days with platelet counts less than $20,000/\mu\text{L}$ were 0.7, 1.4, 1.6, and 2.4 for anti-D, IVIg, oral prednisone, and methylprednisolone respectively. The probabilities of side effects used in the model were 18%, 28%, 12%, and 12% for anti-D, IVIg, oral prednisone, and methylprednisolone respectively.

The authors state that the disutilities (decrements in utility applied to a health state) that were associated with hospital stay, side effects, and ICH were derived using the Health and Activity Limitation Index. The authors did not state from whom the utility decrements were derived. The utility decrements that were assumed in the model were 0.2 per day in hospital, 0.1 for a side effect, and 0.32 for an ICH. The number of days that the side effect and ICH utility decrements were applied to is unstated.

In the base case analysis, the model assumed that the probability of ICH was the same for all strategies (0.1%) regardless of the number of days patients had platelet counts less than $20,000/\mu\text{L}$. In the sensitivity analysis, it was assumed that the probability of ICH was 0.1% per day with platelet counts less than $20,000/\mu\text{L}$ and therefore varied between treatment comparators.

In the base case analysis, the methylprednisolone and IVIg strategies were found to be dominated (fewer QALDs at higher costs). The incremental cost-effectiveness of moving from prednisone to anti-D was found to be \$7,616 per QALD. This is the equivalent of \$2.8 million dollars per QALY. Sensitivity analyses were conducted around all model parameters with the focus on the impact of varying assumptions of the incremental cost-effectiveness of anti-D compared with oral prednisone. The lowest cost per QALD for anti-D compared with prednisone was \$2,616 (equivalent of \$954,400 per QALY). This occurred when the cost of anti-D was assumed to be \$40 per kilogram instead of \$80 per kilogram. The authors state that the cost per QALY of anti-D exceeds "the often quoted values of \$50,000/QALY to \$100,000/QALY."

4.2.3 Hollenberg et al., 1988

Using a 10-year Markov model, Hollenberg et al.²³ compared the cost-effectiveness of immediate splenectomy and IVIg (2 g/kg for induction, 1 g/kg maintenance) in children with chronic ITP.

In the immediate splenectomy group, patients were at risk of operative death, post-surgery sepsis, and sepsis related death. Patients who were not cured after splenectomy switched to IVIg treatment in the model.

Patients who were responsive to the initial IVIg infusion received maintenance IVIg infusions until they were cured or needed a salvage splenectomy after two years. Patients who were unresponsive to the initial infusion were immediately given a splenectomy. Patients who were not cured by splenectomy or IVIg therapy were at risk of trauma that would necessitate a hospitalization and an additional IVIg infusion to prevent hemorrhage.

Sources of the clinical inputs parameters for the model included published literature, an unpublished survey, and expert opinion. Cost parameters were based on “Actual charges and present reimbursement rates in New York City.” The unit cost of IVIg was based on the “wholesale price” (no source was given). Costs were in 1986 US dollars.

The main outcome of the model was percentage of patients who were alive at the end of 10 years. The 10-year costs for the immediate IVIg strategy were estimated to be \$20,964 compared with \$16,913 for the immediate splenectomy group. The model estimated the survival rate to be 98.63% for IVIg and 97.89% for immediate splenectomy. The incremental cost per death avoided for the IVIg group compared with the splenectomy was estimated to be \$540,130.

Multiple sensitivity analyses were conducted. Changing the proportion of patients who were curable by IVIg $\pm 25\%$ varied the incremental cost-effectiveness ratio (ICER) from \$166,000/death avoided to \$1,200,000/death avoided. Changing the cost of IVIg from \$35/g to \$21/g made IVIg dominant. If the cost of splenectomy increased from \$10,000 to \$16,380, IVIg becomes dominant. If children are less than six years old, the IVIg strategy becomes less costly than splenectomy and therefore becomes dominant (less costly, more effective).

No conclusions regarding the cost-effectiveness of the base case model were provided. The report suggests, however, that initial IVIg treatment of younger children with chronic ITP is a cost-effective strategy.

4.2.4 Adams et al., 2001

Using an administrative database, Adams et al.²⁶ estimated the cost-effectiveness of several treatments for childhood ITP. This study was available only as a published abstract. The authors compared anti-D 50 $\mu\text{g}/\text{kg}$, IVIg 0.8 g/kg , and IVIg 1 g/kg over two days. Patients aged 1 to 15 years with a primary diagnosis of ITP or treated for ITP-related sequelae were included in the analysis. The analysis was based on 10-year data (1987 to 1997) from the Nationwide Inpatient Sample (NIS). The authors stated that the NIS is a large US database containing discharge data from 1,000 hospitals in 22 states. The database was used to examine ICH, other hemorrhage, and death by treatment. It appears that lifetime survival was extrapolated to model life years gained, although this was unspecified.

Treatment costs, which were expressed in US dollars, were based on Red Book average wholesale prices with Medicare physician fees. The year that costs were based on was unspecified.

The cost to prevent one ICH was estimated to be \$279,000 for anti-D, \$250,000 for IVIg 0.8 g/kg, and \$616,400 for IVIg 1 g/kg for two days. The cost per life year saved was estimated to be \$4,892 for anti-D and \$4,792 for IVIg 0.8 g/kg. The authors did not conduct an incremental cost-effective analysis. Insufficient information was provided to independently derive these estimates. The authors state that the cost per life year saved estimates “are well within the range of socially cost-effective therapies.”

4.3 Discussion

Several studies have included both costs and outcome comparisons of IVIg versus alternative therapies for ITP. The cost-effectiveness of long-term IVIg treatment versus immediate splenectomy for the treatment of chronic ITP was evaluated by Hollenberg et al.²³ in a 10-year Markov model. The incremental cost-effectiveness of IVIg was estimated to be \$540,130 per death averted. Because the life expectancy of the patients in the model would be long, however, the cost per life year gained would be lower than \$540,130.

Two studies^{24,26} evaluated the costs and outcomes of treatments for childhood ITP by incorporating observational patient level data. Neither study specified whether all children were being treated for the acute form of the disease. Using information presented by Kumar et al., the incremental cost-effectiveness of IVIg compared with anti-D can be calculated as \$889 per day with a platelet count of less than 20,000/ μ L. Adams et al. estimated the average cost-effectiveness ratio of IVIg to be \$4,792 per life year gained.

One study²⁵ evaluated the cost-effectiveness of treatments for acute childhood ITP using a decision analytic model. The model by O’Brien found IVIg to be dominated by anti-D. The incremental cost-effectiveness of anti-D compared with prednisone treatment was estimated to be \$612,000 per QALY. The O’Brien model does have shortcomings. In the base case analysis, the authors assume no difference in the probability of ICH between treatment groups, despite the fact that the prevention of ICH is the primary reason for treatment. Treatment specific probabilities of ICH are included in a sensitivity analysis. The time horizon of the model, however, is limited to the duration of the acute hospitalization. The long-term consequences of ICH, including immediate death, cannot be captured in such a short time.

All the identified evaluations were undertaken from a US perspective and were specific to childhood ITP. One study used quality-adjusted life years (QALYs) as its outcome²⁵ and a time horizon that was too short to capture the long-term consequences of ICH. As a result, there is a need for Canadian-specific economic evaluations of IVIg treatment in children and adults with ITP.

5 ECONOMIC EVALUATION FOR CHILDREN WITH ACUTE ITP

5.1 Methods

5.1.1 Type of evaluation

A cost-utility analysis was conducted using a Markov model for children with acute ITP. A cost-utility analysis (cost per QALY) was used because the QALY captures the life years lost and the quality of life impact of having an ICH.

Because the prevention of ICH is the primary goal of treatment in the model, a secondary cost-effectiveness analysis that examined the incremental cost per ICH avoided was conducted.

5.1.2 Target population

The population entering the model are hospitalized children with ITP and a platelet count of less than 20,000/ μ L. As in O'Brien et al.'s study, children were assumed to weigh 20 kg. This weight was chosen because it corresponded to the average age (5.7 years) of patients in a large published childhood ITP registry.²⁷ This weight was also assumed in the Canadian IVIg treatment guidelines document when estimating the cost of treating childhood ITP.¹²

5.1.3 Comparators

There are five comparators in the model:

- observation (no treatment)
- IVIg (single dose 0.8 g/kg)
- anti-D (single dose 75 μ g/kg)
- prednisone (4 mg/kg per day for four days)
- IV methylprednisolone (30 mg/kg for three days).

The treatment regimens are based on what was assumed in O'Brien et al.'s study.²⁵ A clinical expert confirmed that these dosing regimens are relevant in Canada. The risk of postsplenectomy sepsis is significant, with the incidence of septic mortality ranging from 3% to 11%. The incidence of postsplenectomy sepsis is highest among patients younger than 5 years of age. Splenectomy is reserved for those who have extremely low platelet counts (and therefore, are at risk of bleeding) and who are refractory to pharmacologic management.⁴ Therefore, we are not using splenectomy as a comparator in the model.

5.1.4 Perspective

The analysis was taken from the perspective of a publicly funded health care system. Costs from this perspective include hospital related costs, physician fees for services covered by provincial fee schedules, inpatient and hospital clinic administered drugs, and drugs covered by the provincial formularies for eligible patients. The costs of IVIg and anti-D are part of provincial and territorial health budgets.¹² These costs form part of the payment to Canadian Blood Services

and to Héma-Québec. Indirect costs, such as productivity losses, were not considered in the analysis.

5.1.5 Time horizon

Because ICH has long-term morbidity and mortality consequences, a lifelong time horizon is assumed for the primary outcome of the model. A child who dies from ICH will lose many years of life. A child who survives ICH will have diminished lifetime quality of life. This can only be captured in a lifelong time horizon.

For the secondary outcome (cost per ICH avoided), the time horizon is limited to the duration of the acute ITP episode.

5.1.6 Discount rate

The model uses a lifelong time horizon. Therefore, a 5% discount rate was applied to costs and effects. The discount rate was altered in a sensitivity analysis.

5.1.7 Model structure

The general structure of the acute childhood model was based on the economic model by O'Brien et al.²⁵ The structure was modified to allow for a lifelong time horizon so that the long-term impact of ICH could be captured. We have added a no treatment (observation) strategy, because a clinical expert suggested that this treatment option should be considered. The model begins with children who are hospitalized for an increased risk of serious bleeding events that are associated with platelet counts of less than 20,000/ μ L, for example, ICH (Appendix 5).

The model assumes that all patients, including those who are just observed, are hospitalized until platelet counts reach safe levels. Appendix 5 shows that each treatment group is at risk of an ICH. The probability of ICH occurrence depends on the length of time that patients spend with platelet counts of less than 20,000/ μ L. Patients are also at risk of experiencing medication side effects. Patients who have an ICH are at risk of immediate death. Patients who have an ICH are assigned the additional cost of an ICH hospitalization. Because it is inappropriate to treat Rh negative patients with anti-D, the cost of a blood typing test was applied to the anti-D treatment arm.

After the acute hospitalization, patients who do not die from an ICH during the acute episode enter a Markov model with a cycle length of one year. The Markov model has a lifelong time horizon, as it is run until all patients die or reach the age of 110. Patients are at risk of death during each one-year cycle. Age-specific death probabilities were based on Canadian life tables.²⁸ Age-specific utility values were applied to the patients who were alive in each year of the Markov model. This allows patients to accrue QALYs during the long-term model phase. Patients who experienced ICH during the acute ITP episode but survived are assigned a lower utility value and additional health care costs in each cycle of the long-term Markov model.

5.1.8 Data considerations

Input variables were needed for the decision model. These included clinical variables, cost variables, mortality variables, and utility input variables.

a) Clinical inputs

The main clinical effectiveness input variable in the model is the mean time that patients in each treatment group spend with platelet counts of less than 20,000/ μL . This was estimated using data from trials that were identified in the CADTH clinical review of IVIg in ITP,²⁹ with additional studies identified in O'Brien et al.'s study.²⁵ Only studies with a baseline population of children with platelet counts of less than 20,000/ μL were included in the analysis. A few studies reported the mean time that patients spent with platelet counts of less than 20,000/ μL . Most studies reported the proportion of patients achieving platelet counts greater than 20,000/ μL at different time points after treatment initiation. Data for each treatment were pooled regardless of the dosing used in the trial. In a sensitivity analysis, time with platelet counts less than 20,000/ μL for anti-D is estimated using data from trials using 75 μg dosing only.

To estimate the time spent with platelet counts less than 20,000/ μL , data on the proportion of patients with platelet counts greater than 20,000/ μL at one day, two days, three days, and seven days after therapy initiation were pooled by treatment groups (Appendix 6).

Data were pooled by day for each treatment using random effects meta-analysis.³⁰ Using the proportion of patients with platelet counts greater than 20,000/ μL at the different time points, a "time to platelet count of greater than 20,000/ μL curve" was constructed for each treatment. Based on these curves, the time spent with platelet counts less than 20,000/ μL was estimated for each treatment.

Figure 2 provides an example of how a platelet count curve is used to calculate the mean number of days with platelet counts less than 20,000/ μL for a treatment strategy. The X axis represents the number of days since treatment initiation, while the Y axis represents the proportion of patients with platelet counts greater than 20,000 / μL . The proportion of patients with platelet counts greater than 20,000/ μL , on days 0, 1, 2, 3, and 7, is plotted on the graph. A curve is created assuming a straight line relationship between time points. The area under the curve represents the mean number of days with a platelet count greater than or equal to 20,000/ μL . Calculating the area above the curve provides the mean number of days with platelet counts less than 20,000/ μL .

Figure 2: Example of “time to platelet count greater than 20,000/ μ L curve”

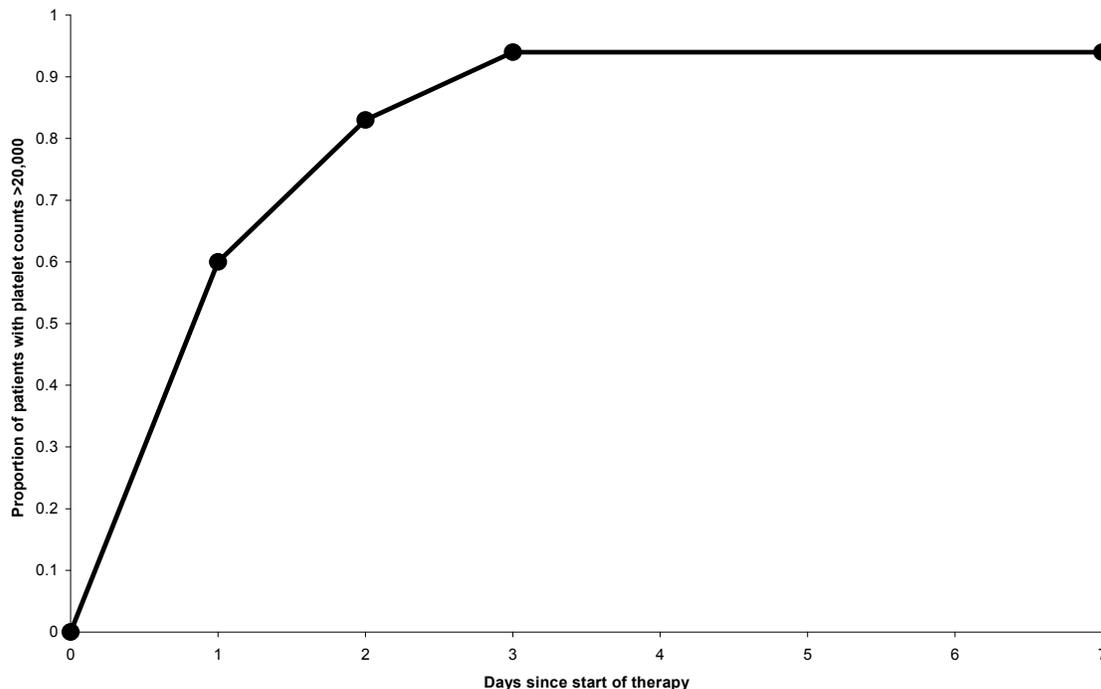


Table 3 shows our pooled estimates of the proportion of patients with platelet counts less than 20,000/ μ L at day 1, day 2, day 3, and day 7 for each treatment group.

The probability of ICH when platelet counts are less than 20,000/ μ L was based on data from Lilleyman’s study.³¹ In a retrospective survey of all cases of ICH in children with ITP in the UK, Lilleyman estimated that ICH occurs in 0.1% of all childhood ITP cases. Later, Lilleyman³² stated that the probability of ICH in the “first few days after diagnosis” is between 0.1% to 0.2%. This range was based on an estimate of the number of potential unreported cases of ICH in the previous study. For the base case model, it was assumed that the probability of ICH was 0.0375% (0.15%/4 days) for each day that the platelet counts were less than 20,000/ μ L. This assumption was altered in the sensitivity analysis.

The probability of side effects for each treatment was based on estimates used in O’Brien et al.’s study. The authors of this study stated that their estimates were based on a literature search and focused on common side effects such as fever, nausea, vomiting, headache, and gastric discomfort.

Table 3: Pooled estimates of proportion of patients with platelet counts less than 20,000/ μ L by day and by treatment and time with platelet counts less than 20,000/ μ L

	Day 1		Day 2		Day 3		Day 7		Days Platelets <20,000/ μ L
	n	Proportion with Platelets >20,000/ μ L (95% CIs)	n	Proportion with Platelets >20,000/ μ L (95% CIs)	n	Proportion with Platelets >20,000/ μ L (95% CIs)	n	Proportion with Platelets >20,000/ μ L (95% CIs)	
IVIg	5	0.60 (0.46, 0.73)	6	0.83 (0.76, 0.91)	6	0.94 (0.88, 1.0)	6	0.94 (0.88, 1.0)	1.34
Anti-D	5	0.59 (0.38, 0.79)	1	0.71 (0.57, 0.85)	1	0.82 (0.69, 0.94)	3	0.91 (0.84, 0.99)	1.83
Prednisone	2	0.31 (0.19, 0.44)	2	0.70 (0.58, 0.82)	2	0.81 (0.70, 0.91)	7	0.93 (0.83, 0.99)	2.10
Methylprednisolone	1	0.37 (0.21, 0.53)	3	0.57 (0.45, 0.69)	2	0.80 (0.64, 0.97)	2	0.94 (0.80, 1.0)	2.18
No therapy	1	0.13 (0.00, 0.34)	2	0.31 (0.10, 0.53)	2	0.65 (0.32, 0.91)	2	0.80 (0.59, 1.0)	3.33

CIs=confidence intervals; IVIg=intravenous immunoglobulin; n=number of studies (Appendix 6).

b) Cost inputs

Table 4 provides the unit costs of treatments used in the model. Also shown are the total costs of each treatment group for treating a 20-kg child. The cost of IVIg and anti-D was provided by Canadian Blood Services and represents prices for fiscal 2008 to 2009. (Mathias Haun, Director, Plasma Products and Services, Canadian Blood Services, Ottawa, ON: personal communication, 2008 Apr). The cost per pill of prednisone and per methylprednisolone 100 mg/5 mL suspension pack were derived from the Ontario Drug Benefit Formulary.³³ The cost of treatment was based on our assumed dosing regimen.

Table 4: Treatment costs

Medication	Unit Cost	Course Cost for 20-kg Child (\$)
IVIg	\$59.19/g	947.04
Anti D	\$75.04 per 300 μ g vial	375.20
Prednisone	\$0.0913 per 50 mg tablet	0.73
Methylprednisolone	\$10.51 per 100 mg/5 mL InjSusp-5 mL package	189.18

Course=treatment regimen (total units of medication given for treatment); InjSusp=injectable suspension.

The cost per ITP hospitalization day (\$892) and the cost for ICH hospitalization (\$18,302) were based on data from the Ontario Case Costing Project.³⁴ The annual post-stroke costs (\$4,624) were based on a Canadian longitudinal analysis of matched diabetic and non-diabetic patients.³⁵ The cost per blood typing test (\$17.72) came from a hospital participating in the Ontario Case Costing Project.³⁶

c) Mortality inputs

Age-specific annual mortality rates were based on the Canadian Life Tables.²⁸ We assumed that the probability of immediate death after ICH was 50% [95% confidence interval (CI) 38% to 62%] as found in a prospective study of stroke outcomes in the UK.³⁷

d) Utilities

The disutility that was applied to side effects (0.10) was based on the value used by O'Brien et al.²⁵ in their model. Age-specific utility values that were used in the long-term phase of the model were based on a study that estimated utility values in the UK general population.³⁸ During the long-term phase of the model, a utility weight of 0.45 was applied to patients who had an

ICH during the acute hospitalization but did not immediately die. This value was based on the mean utility for major stroke reported by Shin et al.³⁹

Table 5 presents a summary of all model variables.

Table 5: Model inputs			
Model Variable	Base Case Value	Distribution	95% CI Based on Distribution and Parameters
ICH probabilities			
Probability of ICH When platelets<20,000/ μ L	0.000375	Beta	(0, 0.0017)
Probability of immediate death after ICH	0.50	Beta	(0.38, 0.62)
Probability of side effects			
IVIg	0.28	Beta	(0.20, 0.37)
Anti-D	0.18	Beta	(0.11, 0.26)
Prednisone	0.12	Beta	(0.06, 0.19)
Methylprednisolone	0.12	Beta	(0.06, 0.19)
Cost variables			
Cost per ITP hospital day	\$892	Gamma	(532, 1,173)
Cost per ICH hospitalization	\$18,302	Gamma	(13,684, 23,600)
Annual cost of ICH	\$4,624	Gamma	(4,453, 4,794)
Side effects	\$10	Gamma	(6, 14)
Utility values			
General population			
Age<25	0.94	No distribution	
25 to 34	0.93	No distribution	
35 to 44	0.91	No distribution	
45 to 54	0.85	No distribution	
55 to 64	0.80	No distribution	
65 to 74	0.78	No distribution	
Utility weight post-ICH	0.45	Beta	(0.33, 0.56)
Disutility for side effects	0.10	Beta	(0.05, 0.16)

CI=confidence interval; ICH=intracranial hemorrhage; ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin.

5.1.9 Uncertainty

Probabilistic analysis was performed to address parameter uncertainty.. In probabilistic analysis, distributions for model variables are specified instead of point estimates. Values from these distributions are randomly drawn simultaneously in a large number of simulations. For each simulation, the costs and effects (QALYs) for all strategies are estimated. Using the simulation results, the probability that each strategy is the most cost-effective can be calculated given a specified willingness-to-pay value. Parameter uncertainty is expressed as cost-effectiveness acceptability curves (CEACs). CEACs present the probability that a strategy is the most cost-effective as a function of willingness to pay for a QALY.

Beta distributions were assigned to model variables that were constrained to values between 0 and 1 (probabilities, utilities). Gamma distributions were assigned to model cost variables (Tables 3 and 5). Parameter uncertainty of the base case results were expressed as CEACs.

One-way sensitivity analyses were conducted on model parameters with structural uncertainty (discount rate, dosing regimens), parameters that represent different subgroups of patients (patient weight) and other key model variables with uncertainty beyond what was captured in the probabilistic analysis (daily probability of ICH).

5.2 Economic Analysis of Acute Childhood ITP: Results

5.2.1 Base case analysis

a) Primary economic analysis (incremental cost per QALY)

Base case model results for the primary economic outcome are presented in Table 6. The strategy with the lowest expected costs is prednisone (\$1,844). The strategy with the highest expected costs is observation (\$2,739), and IVIg has the second highest expected costs (\$2,080). Table 6 shows the costs of treatment (medications and blood products), hospital costs during acute treatment, and costs deriving from cases of ICH (short-term and long-term). IVIg was associated with the highest treatment cost (\$947). IVIg also had the lowest hospitalization cost (\$1,100) and ICH related costs (\$32). The hospital costs were lowest for IVIg because this strategy had the shortest mean time for patients to reach platelet counts less than 20,000/ μ L, leading to the shortest time in hospital.

The observation strategy had the lowest expected QALYs (17.686) while IVIg has the highest expected QALYs (17.6958). This is to be expected, because these two strategies have the highest and lowest time with platelet counts less than 20,000/ μ L and therefore the highest and lowest likelihood of incurring an ICH among the five strategies.

To determine the incremental cost utility, a cost-effectiveness efficiency frontier must be constructed by first determining which strategies are dominated by other strategies. If a strategy results in more QALYs and less costs than another strategy, it is considered to be dominant. The incremental costs and QALYs of non-dominated strategies are plotted and make up the frontier. Starting from the least costly strategy, incremental cost utility ratios (ICURs) are calculated moving from one strategy on the frontier to the next. The cost-effectiveness efficiency frontier for the base case analysis of the primary outcome is shown in Figure 3.

The observation treatment strategy is dominated by all other strategies. The methylprednisolone strategy is dominated by the anti-D strategy (anti-D provides more QALYs and is less costly than methylprednisolone). This leaves prednisone, anti-D, and IVIg on the efficiency frontier. The incremental cost per QALY to move from the prednisone strategy to the anti-D strategy is \$53,333. The incremental cost per QALY to move from the anti-D strategy to the IVIg strategy is \$56,000. Based on these results, IVIg can be considered to be a cost-effective strategy if a decision maker is willing to pay \$56,000 or more for a QALY. Furthermore, prednisone can be considered to be a cost-effective strategy if a decision maker is willing to pay less than \$53,333

for a QALY. If a decision maker is willing to pay \$53,333 and \$56,000, then anti-D can be considered to be a cost-effective strategy.

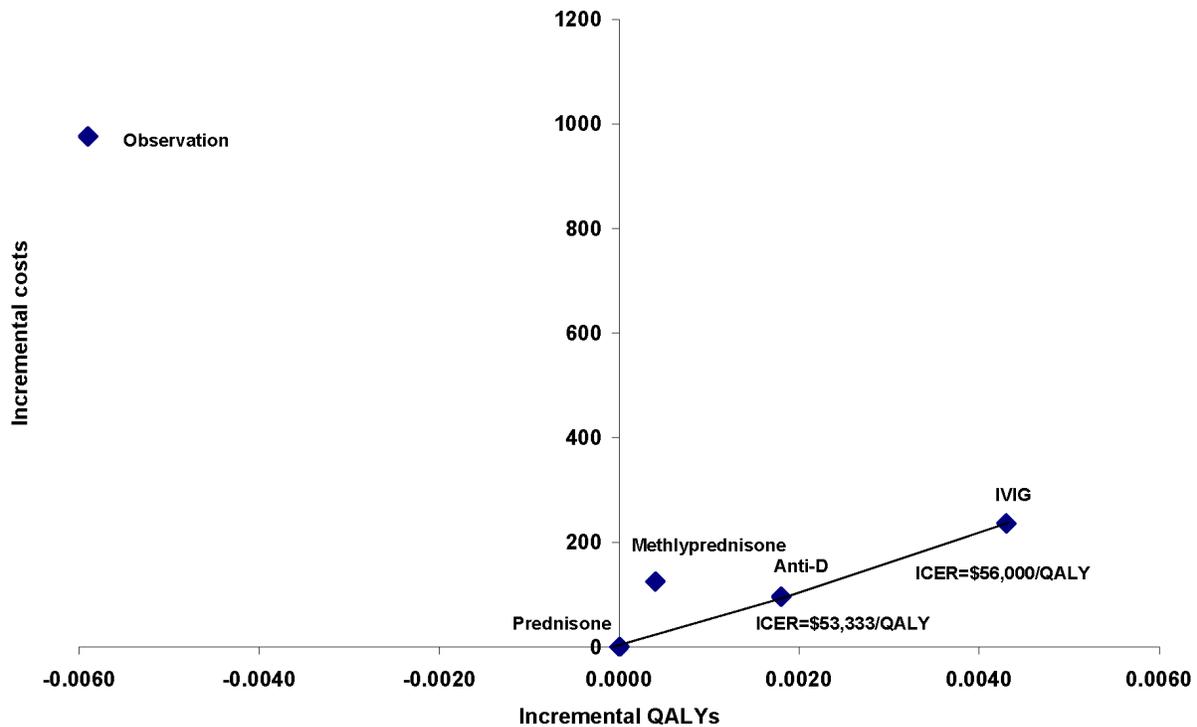
b) Secondary economic analysis (incremental cost per ICH avoided)

Table 7 presents results for the secondary outcome (cost per ICH avoided). The observation strategy had the highest number of ICHs while IVIg had the lowest number. The number of expected ICHs for these strategies was 12.51 per 10,000 patients and 5.02 per 10,000 patients respectively. The estimated ICHs for the prednisone, methylprednisolone, and anti-D strategies were 8.18, 7.89, and 6.86 per 10,000 patients respectively. The methylprednisolone and observation strategies were dominated by other strategies. The incremental cost per ICH avoided moving from the prednisone strategy to the anti-D strategy was \$732,789. The incremental cost per ICH avoided moving from the anti-D strategy to the IVIg strategy was \$760,778.

Treatment	Treatment Costs	Hospital Costs	ICH Costs	Total Costs	QALYs	Incremental		
						Costs	QALYs	ICUR
Prednisone	\$1	\$1,790	\$53	\$1,844	17.6915	Reference	Reference	Reference
Methylprednisolone	\$189	\$1,729	\$51	\$1,969	17.6919	\$125	0.0004	Dominated
Anti-D	\$375	\$1,521	\$44	\$1,940	17.6933	\$96	0.0018	\$53,333
IVIg	\$947	\$1,100	\$32	\$2,080	17.6958	\$236	0.0043	\$56,000
Observation	\$0	\$2,739	\$81	\$2,820	17.6856	\$976	-0.0059	Dominated

ICH=intracranial hemorrhage; ICUR=incremental cost utility ratio; QALY=quality-adjusted life year.

Figure 3: Cost-effectiveness efficiency frontier



ICER=incremental cost-effectiveness ratio; IVIg=intravenous immunoglobulin; QALY=quality-adjusted life year.

**Table 7: Base case results — Secondary economic analysis
(incremental cost per ICH avoided)**

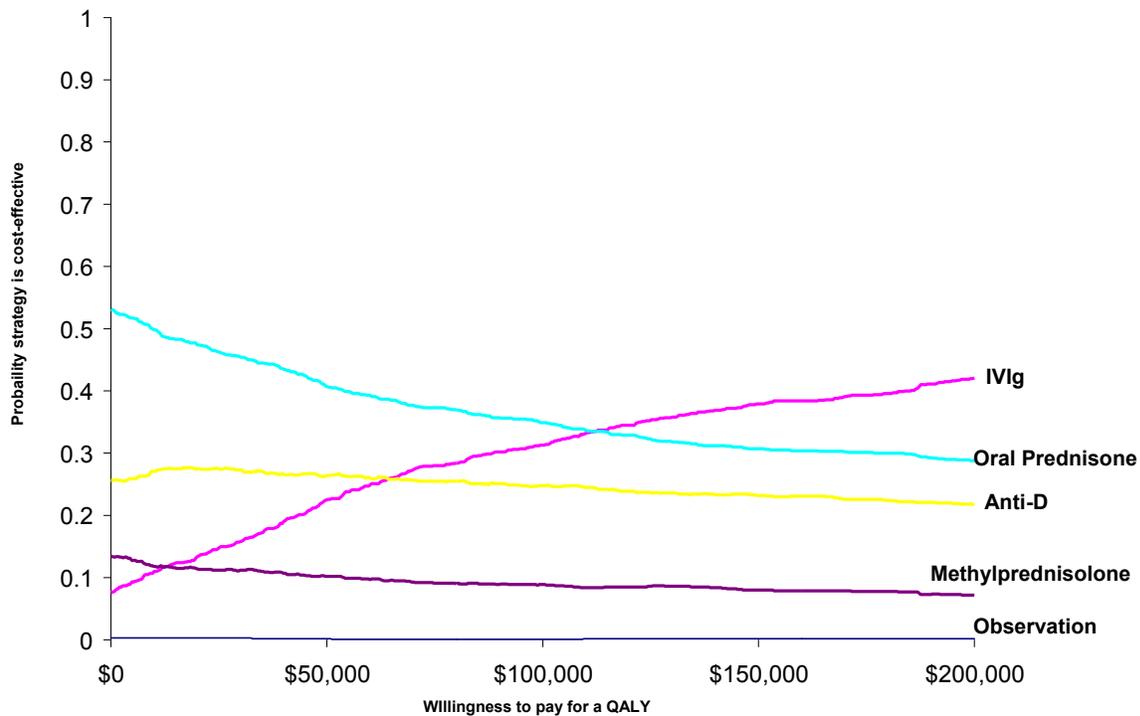
Treatment	Total Costs	ICH Per 10,000	Incremental Costs	Incremental ICH per 10,000	ICER (Incremental cost per ICH avoided)
Prednisone	\$1,844	8.18	Reference	Reference	Reference
Methylprednisolone	\$1,969	7.89	\$125	-0.29	Dominated
Anti-D	\$1,940	6.86	\$98	-1.32	\$732,789
IVIg	\$2,080	5.02	\$240	-3.16	\$760,778
Observation	\$2,820	12.51	\$971	4.33	Dominated

ICH=intracranial hemorrhage; ICER=incremental cost-effectiveness ratio; IVIg=intravenous immunoglobulin.

5.2.2 Probabilistic sensitivity analysis

Figure 4 presents the CEACs for each of the five strategies. The X axis represents society’s maximum willingness to pay for a QALY. The Y axis represents the probability that a given strategy is the most cost-effective. Prednisone has the highest probability of being cost-effective up to a willingness to pay of \$110,200 per QALY. IVIg has the highest probability of being cost-effective at ceiling ratios greater than \$112,000. At a ceiling ratio of \$100,000 per QALY, the probability that IVIg is cost-effective is 0.31.

Figure 4: Cost-effectiveness acceptability curves



IVIg=intravenous immunoglobulin; QALY=quality-adjusted life year.

5.2.3 One-way sensitivity analysis

One-way sensitivity analyses were conducted on model parameters and assumptions made in the primary analysis (Table 8). Because the Observation and Methylprednisolone strategies were dominated in all sensitivity analyses, their results are not provided. Lowering the discount rate lowers the ICUR of IVIg compared with anti-D. Changing the discount rate from 5% to 3% changes the ICUR to \$36,335 per QALY. Changing the discount rate to 0% changes the ICUR to \$13,019 per QALY.

The time with platelet counts less than 20,000/ μ L for anti-D changes from 1.84 days to 1.54 days if effectiveness data for anti-D are based solely on studies of 75 μ g. This has a large impact on the cost-effectiveness results because anti-D replaces prednisone as the reference strategy on the efficiency frontier. The incremental cost-utility of IVIg relative to anti-D is \$383,474 per QALY in this scenario.

Assuming different dosing regimens for IVIg has a large impact on the results. Canadian IVIg guidelines¹² suggested that one dose of IVIg 0.8 g/kg to 1 g/kg is appropriate for acute childhood ITP, with a second dose given if platelet levels are not greater than 20,000/ μ L. If IVIg dosing is changed from 0.8 g/kg to 1 g/kg, the ICUR moving from anti-D to IVIg is \$150,664 per QALY. A clinical expert (DP) suggested that 50% of IVIg patients may receive a second 0.8 g/kg dose. With this assumption, the incremental cost utility of IVIg relative to anti-D becomes \$245,396 per QALY.

Assuming different daily probabilities of ICH when platelet counts are less than 20,000/ μ L affects results. If the per-day probability of ICH is assumed to be 0.001 instead of 0.000375, the cost per QALY of IVIg becomes \$17,882. If this probability is assumed to be 0.0005, the cost per QALY of IVIg becomes \$40,650. If the probability of ICH is assumed to be 0.0001, the cost-effectiveness of IVIg becomes \$229,740.

The results are sensitive to the assumed weight of the cohort. Table 8 presents the cost-utility results, assuming different patient weights with corresponding ages. The average patient weight by age was derived from Centers for Disease Control and Prevention data.^{40,41}

If the cohort is assumed to weigh 12.25 kg (2 years old), IVIg becomes the dominant strategy (IVIg results in fewer costs and more QALYs than all other strategies). If the cohort is assumed to weigh 16.15 kg (4 years old), the ICUR of IVIg is \$12,438. If the patient weight is 25.70 kg (8 years old), the incremental cost per QALY for IVIg is \$118,648. Assuming a patient weight of 41.5 kg (12 years old) increases the cost per QALY of IVIg to \$294,560.

Table 8: One-way sensitivity analyses

		\$/QALY		
		Prednisone	Anti-D	IVIg
Base case		reference	\$53,333	\$56,000
Discount rate	0%	reference	\$12,443	\$13,019
	3%	reference	\$34,917	\$36,335
Anti-D 75 µg effectiveness data only		dominated	reference	\$383,474
IVIg dosing	1g/kg	reference	\$53,333	\$150,664
	assume 50% get 2 nd IVIg dose	reference	\$53,333	\$245,396
Probability of ICH per day	0.0001	reference	220,288	\$229,740
	0.0005	reference	\$39,060	\$40,650
	0.001		\$17,105	\$17,882
Weight of child (corresponding age)				
	12.25 kg (2 years old)	dominated	dominated	dominates
	16.15 kg (4 years old)		dominated	\$12,438
	20.45 kg (6 years old)	reference	dominated	\$60,004
	25.70 kg (8 years old)	reference	dominated	\$118,648
	32.25 kg (10 years old)	reference	dominated	\$192,784
	41.15 kg (12 years old)	dominated	dominated	\$294,560
	50 kg (14 years old)	reference	dominated	\$397,695

ICH=intracranial hemorrhage; IVIg=intravenous immunoglobulin; QALY=quality-adjusted life year.

5.3 Discussion

In this primary Canadian economic model evaluating treatments for acute childhood ITP, the incremental cost utility of IVIg was estimated to be \$56,000 per QALY. Therefore, if society is willing to pay up to \$100,000 for a QALY, IVIg may be considered to be cost-effective for treating 20-kg children with acute ITP. The cost-effectiveness results depend on the probability of ICH as a function of the number of days patients have platelet counts of less than 20,000/µL. In O'Brien et al.'s model,²⁵ the per-day probability of ICH is assumed to be 0.1%. This was based on commonly cited data presented by Lilleyman.³¹ This is likely, however, to be an overestimation of the per-day ICH probability, because it represents the probability of ICH found for an entire episode of acute childhood ICH, which can last for many days. In our current model, it was assumed that the daily probability of ICH with platelet counts less than 20,000/µL was 0.0375%. This was based on Lilleyman's estimation that the probability of ICH in the "first few days of ITP" was 1% to 2%.³² As shown in our sensitivity analysis, when higher rates of ICH are assumed, the cost-effectiveness of IVIg becomes more favourable.

Cost-effectiveness also depends on assumptions pertaining to patient weight, because IVIg dosing is weight-dependent. If patient weight is assumed to be 25.70 kg or more, the incremental cost-effectiveness of IVIg increases to more than \$100,000 per QALY. If patient weight is equal or less than 12.25 kg, then IVIg dominates (less costly and produces more QALYs) all other strategies.

The main limitation of this model is the lack of direct evidence that treatment with IVIg leads to fewer ICH compared with alternative therapies. Because ICH is a rare event, conducting randomized trials to capture this outcome would require substantial numbers of participants and resources, and might explain why this has not been undertaken. One role of economic modelling is to take intermediate outcomes such as time with platelet counts less than 20,000/ μ L and estimate how that translates into final outcomes such as ICH. Another limitation is that some clinicians may use high-dose pulse dexamethasone instead of prednisone. High-dose dexamethasone was excluded in the model because of a lack of published clinical effectiveness data regarding the treatment of acute ITP.

6 ECONOMIC ANALYSIS FOR ADULTS WITH CHRONIC ITP

6.1 Methods

6.1.1 Type of evaluation

A cost-utility analysis was conducted using a Markov model for adults with chronic ITP.

6.1.2 Target population

The starting population of the model was a hypothetical cohort of adult patients with ITP at the age of 35 years, with a weight of 70 kg and a platelet count of less than 20,000/ μ L.

6.1.3 Comparators

The adult patients with chronic ITP were treated with IVIg at a dose of 1 g/kg per day for two consecutive days according to the guidelines in Canada¹² or with prednisone at a dose of 1 mg/kg of weight per day for a month according to the recommendation by the American Society of Hematology and the published studies.^{13,42,43} The side effects were considered nominal for a one-month treatment with prednisone and thus excluded in the model. Because insufficient information is available on anti-D treatment for adult ITP, anti-D treatment strategy was excluded from the analysis.

6.1.4 Perspective

The project was conducted from the perspective of a publicly funded health care system.

6.1.5 Time horizon

The time horizon for the model was lifetime.

6.1.6 Modelling

The Markov model was developed based on the results of a clinical and economic review²⁹ and on the advice from clinical experts (Appendix 7). The distribution of the study cohort in the two Markov states (remission and refractory) at cycle 0 was determined by the initial response to the IVIg or prednisone strategies (including complete and partial remission). Complete and partial remission is defined as a platelet count greater than 50,000/ μ L, while refractory is defined as platelet count less than 50,000/ μ L.^{44,45} Refractory patients have persistent low platelet counts, are unlikely to be cured, and are at the greatest risk of death. In this model, refractory patients remained in that state, underwent splenectomy, or died of causes other than ITP. After splenectomy, patients achieved post-surgery remission or remained in a post-surgery refractory state. The length of a cycle is one year. The duration of the treatments were implicitly incorporated into the model by accounting for the cycle length and available transition probabilities based on cycle length.

6.1.7 Data considerations

Clinical probabilities for the model were derived from the studies that were identified in a systematic literature review²⁹ using a random-effect meta-analysis. Table 9 shows that the initial response was estimated to be 0.76 for the IVIg strategy^{44,46-49} and 0.74 for the prednisone strategy.^{42,43,45,48,50-52} The probability of relapse within the first year after initial response was estimated to be 0.49 for the IVIg strategy^{44,46} and 0.52 for the prednisone strategy.⁴² The long-term relapse rate was derived from the only available study and assumed to be the same for IVIg and prednisone strategies.⁴²

The probability of splenectomy was 0.64 in patients who were treated with IVIg⁵³ and 0.75 in patients who were treated with prednisone.^{42,43,45,50} The initial response to splenectomy (including complete and partial remission) was 0.85.^{42,43,45,48,50-52,54,55} The long-term response was derived from the only available study (Table 10),⁴² and the response is irrespective of the comparator.

Age-specific mortality rates were used for patients achieving complete or partial remission based on the Canadian Life Tables⁵⁷. Although ICH is not a concern for adults with chronic ITP, the mortality rate is significantly higher for the patients who are refractory to treatments. In this model, the mortality rate for patients with refractory ITP was 0.028, the midpoint of the range estimated by Cohen et al.⁵⁶

Table 9: Model inputs

Variables	Value	95% CI*	Sources
Probabilities			
Initial response to IVIg	0.76	0.63 to 0.90	44,46-49
Relapse in first year after initial response to IVIg	0.49	0.35 to 0.63	44,53
Splenectomy after IVIg treatment	0.64	0.42 to 0.86	53
Initial response to prednisone	0.74	0.64 to 0.83	42,43,45,48,50-52
Relapse in first year after initial response to prednisone	0.52	0.44 to 0.60	42
Splenectomy after prednisone treatment	0.75	0.63 to 0.86	42,43,45,50
Initial response to splenectomy	0.85	0.80 to 0.90	42,43,45,48,50-52,54,55
Death in refractory ITP	0.028	0.016 to 0.040	56
Costs (in 2007 Canadian dollars)			
IVIg, per gram	59.19	51 to 64	
Prednisone, per 50 mg tablet	0.0913		
Splenectomy	11,709	3,251 to 85,452	
Utilities			
General population, age, years			
<25	0.94		
25 to 34	0.93		
35 to 44	0.91		
45 to 54	0.85		
55 to 64	0.80		
65 to 74	0.78		
>74	0.73		
Utility weight for refractory ITP	0.98		56

95% CI=95% confidence interval; ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin.

*The plausible ranges were used for costs and utilities.

Table 10: Long-term relapse rates associated with IVIg, prednisone, and splenectomy

Year	Probability of Relapse			Source
	IVIg	Prednisone	Splenectomy	
1	0.49	0.52	0.15	42
2	0.69	0.69	0.27	
4	0.75	0.75	0.33	
6	0.79	0.79	0.35	

IVIg=intravenous immunoglobulin.

The cost of IVIg was \$59.19 per gram, varying from \$51 to \$64 per gram in Canada according to the publication presenting guidelines on the use of IVIg.¹² The cost of prednisone was derived from the Ontario Drug Benefit Formulary.³³ According to our assumed dosing regimen for an adult ITP patient with a weight of 70 kg, the cost for IVIg and prednisone was \$8,287 and \$4 respectively. The cost of splenectomy (\$11,709) was based on the Ontario Case Costing Initiative.³⁶ All costs were discounted at 5% for the base case analysis.

Age-specific utility values based on a study conducted in the UK general population were applied to remission and post-splenectomy remission states. There is no published study reporting the utilities related to the different health states in ITP. The utility weight for the refractory state was assumed to be 0.98. This weight was then multiplied by the age-specific general population utility value to calculate the age-specific refractory state utility, as in the method used by Cohen et al.⁵⁶ All utilities were discounted at 5% for the base case analysis.

6.1.8 Discounting

In accordance with CADTH guidelines, costs and effects were discounted at 5% annually. A sensitivity analysis was done using 0% and 3% discount rates.

6.1.9 Uncertainty

Probabilistic analysis was performed to address parameter uncertainty. In this model, beta distributions were assumed for all probability variables and the utility weight of refractory ITP. No distribution was applied for those time-dependent variables including general population mortality, long-term relapse rates associated with IVIg, prednisone, and splenectomy, and general population utilities. Gamma distributions were assumed for the cost of splenectomy, while the cost of IVIg or prednisone was assumed to be fixed (Table 11). Uncertainty was expressed as CEACs. Given the uncertainty about the threshold value of willingness to pay for a QALY gained, CEACs were constructed to show the probabilities that IVIg (or prednisone) was more cost-effective than prednisone (or IVIg) over a range of willingness-to-pay values.

Table 11: Distributions for model inputs		
Variables	Point Estimate	Distribution
Probabilities		
Initial response to IVIg	0.76	Beta ($\alpha=27.8, \beta=8.7$)
Relapse in first year after initial response to IVIg	0.49	Beta ($\alpha=22.4, \beta=23.3$)
Splenectomy after IVIg treatment	0.64	Beta ($\alpha=10.9, \beta=6.2$)
Initial response to prednisone	0.74	Beta ($\alpha=55.2, \beta=19.9$)
Relapse in first year after initial response to prednisone	0.52	Beta ($\alpha=69.2, \beta=63.8$)
Splenectomy after prednisone treatment	0.75	Beta ($\alpha=43.0, \beta=14.6$)
Initial response to splenectomy	0.85	Beta ($\alpha=179.8, \beta=31.4$)
Death in refractory ITP	0.028	Beta ($\alpha=20.3, \beta=704.8$)
Costs		
Splenectomy	11,709	Gamma($\alpha=24.7, \lambda=0.002$)
Utilities		
Utility weight for refractory ITP	0.98	Beta ($\alpha=72.5, \beta=27.5$)

ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin.

6.2 Results

6.2.1 Base case analysis

In the base case analysis, the costs of IVIg and prednisone were \$8,287 and \$4 respectively (Table 12). The cost of splenectomy was \$10,213 for the IVIg strategy and \$10,426 for the prednisone strategy. The total costs of the IVIg strategy were \$8,070 more than the prednisone strategy. The incremental QALYs for the IVIg strategy compared with the prednisone strategy were 0.003. The ICER of the IVIg strategy compared with the prednisone strategy was \$2,690,000/QALY.

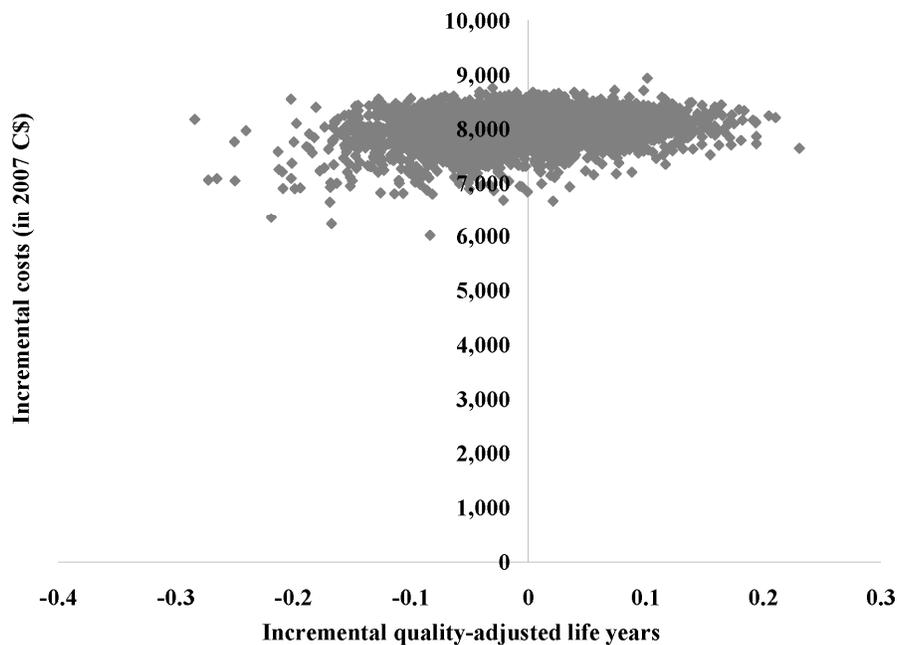
	Costs (in 2007 Canadian dollars)			QALY	ICER
	Treatment	Splenectomy	Total		
Prednisone	\$4	\$10,426	\$10,430	11.9385	
IVIg	\$8,287	\$10,213	\$18,500	11.9415	\$2,690,000

ICER=incremental cost-effectiveness ratio; IVIg=intravenous immunoglobulin; QALY=quality-adjusted life year.

6.2.2 Probabilistic sensitivity analysis

Figure 5 shows that approximately 45% of the samples fell in the upper left quadrant of the cost-effectiveness plane where IVIg was dominated by prednisone (fewer QALYs at higher costs). The ICERs for the remaining samples in the upper right quadrant of the plane ranged from \$33,142/QALY to \$119,453,839/QALY.

Figure 5: Incremental cost-effectiveness of IVIg compared with prednisone



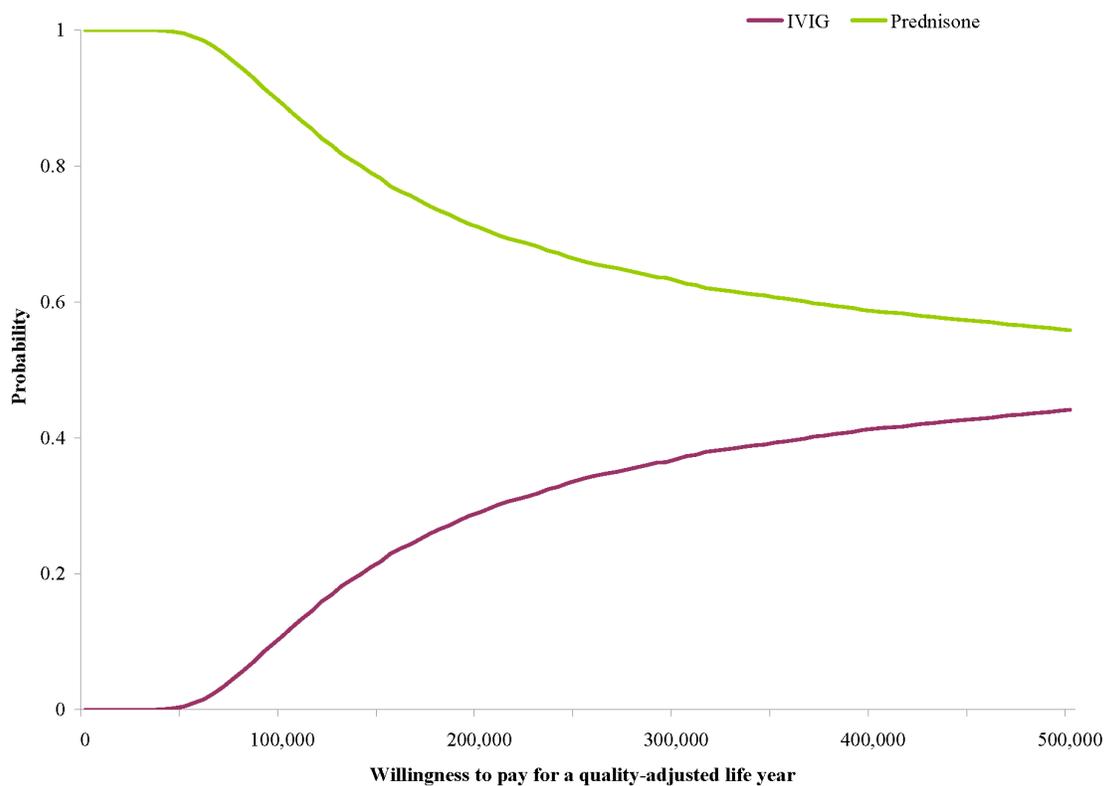
IVIg=intravenous immunoglobulin.

The CEAC (Figure 6) shows the probability that prednisone is more cost-effective than IVIg equals 1 if the willingness to pay for a QALY is less than \$30,000. The probability that IVIg is more cost-effective is 0.44 if the willingness to pay for a QALY increases to \$500,000.

6.2.3 One-way sensitivity analyses

Table 13 shows that the ICER of the IVIg strategy compared with the prednisone strategy was \$551,006/QALY and \$1,400,000/QALY when the discount rates were 0% and 3% respectively.

Figure 6: Cost-effectiveness acceptability curves



IVIg=intravenous immunoglobulin.

When different time horizons were used in the sensitivity analysis, the IVIg strategy was dominated by the prednisone strategy, or the ICERs of IVIg versus prednisone were high.

When the utility weight for refractory ITP decreased from approximately 1.0 to 0.4, the ICER of the IVIg strategy compared with the prednisone strategy decreased from \$2,881,785/QALY to \$1,047,922/QALY.

Other variables had minimal or no impact on the ICER.

Table 13: One-way sensitivity analyses				
Variable	Value	Incremental Costs	Incremental QALYs	ICER*
Base case		\$8,070	0.0030	\$2,690,000
Discount rate	0%	\$8,210	0.0149	\$551,006
	3%	\$8,120	0.0058	\$1,400,000
Time horizon, years	2	\$7,324	0.0008	\$9,155,000
	6	\$7,971	-0.0028	Dominated
	10	\$8,067	-0.0033	Dominated
	40	\$8,070	0.0027	\$2,988,889
Utility weight for refractory ITP	1.0	\$8,069	0.0028	\$2,881,785
	0.8	\$8,069	0.0044	\$1,833,863
	0.6	\$8,069	0.0061	\$1,322,787
	0.4	\$8,069	0.0077	\$1,047,922

ICER=incremental cost-effectiveness ratio; ITP=idiopathic thrombocytopenic purpura; QALYs=quality-adjusted life years.

*Intravenous immunoglobulin strategy was compared with prednisone strategy.

6.3 Discussion

This study compared the lifetime costs and effectiveness of two treatment strategies for adult chronic ITP using a Markov model. In the base case analysis, IVIg gained more QALYs at a significantly higher cost compared with prednisone. The ICERs were unfavourable for IVIg in the deterministic and probabilistic sensitivity analyses. This is the first economic evaluation of IVIg as treatment of adult ITP based on the best available clinical evidence with methodological rigour.

IVIg quickly increases platelet counts to a clinically acceptable level (greater than 20,000/ μ L), reducing the risk of severe bleeding; for example, ICH. This effect is important when treating acute ITP, which occurs more often in children. In contrast, based on our meta-analysis of clinical studies, the initial response rate to IVIg and prednisone in adults with chronic ITP was similar. Because there is no significant difference in long-term effectiveness between the treatments, IVIg demonstrated limited advantages at a higher cost compared with prednisone in treating adults with chronic ITP.

There are two limitations of our evaluation. First, the clinical evidence from head-to-head comparisons of IVIg and prednisone is limited. Most, if not all, of the clinical trials compared different dosages of IVIg in the treatment of chronic ITP in adults. These studies were conducted over a short duration, making it difficult to estimate the long-term effectiveness of IVIg. Second, the ICERs were sensitive to the utilities that were associated with different health states of chronic ITP. The same utility for each health state was assumed in both treatments because of a lack of empirical evidence. If the impact on utilities differs between two treatments, the ICERs could be changed in favour of the treatment with greater improvement in the utilities. This might have implications for future research, with priority being directed to utility measurement in chronic ITP.

Based on our review of the economic data and primary modelling, our findings suggest that compared with prednisone, IVIg is unlikely to be a cost-effective treatment for adults with

chronic ITP, unless decision makers are willing to pay more than \$500,000 for a QALY. It is necessary and important to obtain more empirical evidence of the long-term effectiveness of treatments and the impact on health-related quality of life in adult patients with chronic ITP.

7 HEALTH SERVICE IMPACT

7.1 Population Impact

7.1.1 Methods

Several steps were taken to estimate the number of Canadians with ITP. First, prevalence and incidence estimates were abstracted from studies that were identified through a targeted literature search. Next, prevalence and incidence rates were applied to age and gender specific Canadian population estimates.⁵⁸ Finally, the estimates were broken down by the number of adult and childhood cases. Childhood cases were defined as those occurring in individuals between 0 to 14 years of age. This cut-off was chosen because it was the most commonly used in the identified incidence and prevalence studies.^{2,3,7}

No Canadian specific incidence or prevalence studies were found. Therefore, the incidence and prevalence rates of other countries were assumed to be transferable to Canada.

The number of chronic ITP cases was based on age- and gender-specific prevalence rates that were estimated by Feudjo-Tepie et al.⁷ and applied to Canadian population numbers. An overall prevalence of 20.3 per 100,000 was estimated in this study.

Zeller et al.² estimated the annual incidence of acute childhood (ages 0 to 14 years) ITP to be 4.8 per 100,000 using registry data from Nordic countries. This was used to estimate the number of cases of acute childhood ITP in Canada.

The incidence of ITP in adults (aged 15 years or older) in Denmark was estimated to be 2.64 per 100,000.³ This rate was used to estimate the number of adult acute ITP cases in Canada.

7.1.2 Results

Table 14 presents the estimated number of ITP cases in Canada. The number of chronic ITP cases in Canada is estimated to be 6,672. Most of these are adult cases (6,090). The number of annual acute childhood ITP cases in Canada is estimated to be 268, while the number of acute adult ITP cases is estimated to be 695. The number of acute adult ITP cases was based on information from a study measuring the overall incidence of adult ITP. Many of these cases would likely have evolved into chronic adult ITP.

Table 14: Estimated annual number of cases of ITP		
	ITP Chronic	ITP Acute
Adults (15 years of age and older)	6,090	695
Children (0 to 14 years of age)	582	268
Total	6,672	963

ITP=idiopathic thrombocytopenic purpura

7.2 Budget Impact Analysis

The costs of IVIg are part of provincial and territorial health budgets.¹² These costs are rolled up as part of the payment to Canadian Blood Services and to Héma-Québec. Therefore, IVIg costs are not reflected in hospital budgets or in provincial drug formulary budgets.

The budget impact of IVIg for the treatment of ITP was estimated in two ways. First, the current annual cost of IVIg for ITP in Canada is estimated using published Canadian IVIg utilization data.⁵⁹ Second, the potential budget impact assuming that everybody in Canada with ITP is treated with IVIg is estimated.

7.2.1 Estimate of current annual cost of IVIg for treatment of ITP

Two steps were taken to estimate the annual cost of IVIg for ITP treatment in Canada. First, the total annual cost of IVIg in Canada was estimated. Second, the total annual IVIg costs were multiplied by the proportion of total grams of IVIg that were used for ITP in Canada. Several sources of data were used in these calculations.

According to the most recent annual report, 2.52 million grams of IVIg were used from Canadian Blood Services in fiscal year 2006 to 2007.⁶⁰ In fiscal year 2005 to 2006, an additional 0.98 million grams of IVIg were used from Héma-Québec.⁵⁹ Thus, the current annual IVIg use across Canada is 3.5 million grams. Assuming a cost of \$59.19 per gram, the total annual cost of IVIg in Canada can be estimated to be \$207.2 million (3.5 million × \$59.19).

Constantine et al.⁶¹ estimated IVIg use (in grams) by indication for Atlantic Canada health care facilities. During a six-month period in 2003 to 2004, the authors found that 17.3% of all IVIg was used for ITP.

Applying Constantine et al.'s estimates,⁶¹ the annual cost of IVIg for the treatment of ITP is estimated to be \$35.8 million (\$207.2 million × 17.3%).

7.2.2 Estimate of budget impact if all patients ITP were treated with IVIg

Steps were taken to estimate the potential budget impact if everyone in Canada with ITP was treated with IVIg. First, the annual number of patients in Canada who could be treated for ITP was estimated based on published prevalence and incidence data. Second, a targeted literature search was used to identify Canadian recommendations for IVIg treatment regimens. Third, using treatment regimens, assumptions about the cost of IVIg, and average patient weight, the

annual treatment regimens for acute and chronic ITP were estimated for children and adults. Finally the annual per patient treatment costs were multiplied by the number of people in Canada with ITP to estimate the potential budget impact of IVIg if all patients were treated.

The number of people in Canada with ITP by age group was estimated (Table 14).

Treatment regimens for ITP were based on the recommendations that were published in guidelines for IVIg use in hematologic conditions.¹² These guidelines were developed by a Canadian expert panel.

Table 15 presents recommendations and assumptions made for ITP treatment regimens. The guidelines published by Anderson et al.¹² recommended a treatment regimen for adults with chronic ITP post-splenectomy. This recommendation was assumed for chronic adult ITP. It was assumed that children with chronic ITP would need one maintenance dose per year.

Table 15: Treatment regimens for ITP		
	Treatment Recommendation	Assumption Made for Analysis
Initial (acute) adults and children	1 dose 0.8 g/kg to 1.0 g/kg with second dose given within 48 hours if platelets <20,000/ μ L	1 dose 0.9 g/kg, 50% of patients need second dose
Maintenance (chronic) adults	1 dose of 0.4 g/kg to 1.0 g/kg may be needed every 3 to 8 weeks	1 dose 0.7 g/kg every 6 weeks (8.7 treatments per year)
Maintenance (chronic) children	1 dose 0.8 g/kg to 1.0 g/kg with second dose given within 48 hours if platelets <20,000/ μ L	1 dose 0.9 g/kg, 50% of patients need second dose

ITP=idiopathic thrombocytopenic purpura.

Based on the assumed annual treatment regimens for ITP and a cost of \$59.19 per gram of IVIg, the annual cost of patient treatment was estimated (Table 16).

Table 16: Annual per patient treatment cost by population and type of treatment		
	Initial (Acute)	Maintenance (Chronic)
ITP		
Adults	\$5,593	\$26,931
Children	\$1,598	\$1,598

ITP= idiopathic thrombocytopenic purpura.
*Assume 20 kg for children, 70 kg for adults.

To estimate the potential annual budget impact, the annual IVIg cost for adults and children was multiplied by the number of ITP patients.

Estimates of the potential budget impact of IVIg if all ITP patients were treated appear in Table 17. The potential budget cost for treating all ITP patients with IVIg is estimated to be \$191.64 million. Most of this estimate is applicable to adult patients (\$190.75 million). Table 18 presents estimates of annual budget impact based on different assumptions about the proportion of ITP patients who would be treated with IVIg.

Table 17: Estimate of potential annual budget impact of treating ITP with IVIg in Canada in millions (\$)

	Initial (Acute)	Maintenance (Cohort)	Total
ITP			
Adults	\$34.49	\$164.01	\$198.08
Children	\$ 0.43	\$0.93	\$1.36
Adults and children	\$33.26	\$164.94	\$191.64

ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin.

Table 18: Estimate of potential annual budget impact in Canada in millions (\$) by proportion of ITP patients treated with IVIg

Proportion treated with IVIg	Estimated Annual cost (\$)
1.00	199.43
0.90	179.49
0.80	159.55
0.70	139.60
0.60	119.66
0.50	99.72
0.40	79.77
0.30	59.83
0.20	39.89
0.10	19.94
0.00	0.00

ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin.

7.3 Ethical and Social Issues

7.3.1 Methods

Two reviewers (KC and NA) selected papers that were identified in the clinical and economic reviews for planning, implementation, utilization, equity, legal, regulatory, ethical, and psychosocial content based on the data extraction form established a priori (Appendix 8). Both reviewers (KC and NA) independently extracted information regarding planning, implementation, utilization, equity, and legal, regulatory, ethical, and psychosocial issues.

Content that was specific to trial-level decisions or operations was not extracted, because they were considered to be irrelevant according to the scope of this project (for example, whether the authors asked for or obtained trial participants' informed consent). The focus of extraction was on content related to study results or general statements regarding the use of IVIg outside the study. None of the studies was undertaken for the purpose of documenting planning, implementation, utilization, equity, legal, regulatory, ethical, and psychosocial issues. Once extracted, data were grouped according to the category of response.

The results were reviewed by one policy expert (MG) and two clinical experts (DP and CC). Reviewers' comments were summarized.

7.3.2 Results

Thirty articles^{11,23-26,44,46,47,49,53,62-81} met the criteria for planning, implementation, utilization, equity, legal, regulatory, ethical, and psychosocial content. Final results consisted of 26 clinical^{11,44,46,47,49,53,62-81} and four economic²³⁻²⁶ studies.

a) Adverse events

The 26 clinical trials^{11,44,46,47,49,53,62-81} and three²³⁻²⁵ of the four economic evaluations discussed the issue of the side effects experienced by a patient after IVIg administration, in a specific trial, or related to IVIg administration in general.

The reported incidence of adverse events ranged from 3% to 82% and was sometimes described solely qualitatively (for example, infrequent). The most commonly described adverse events were abdominal pain, asthenia, chills, dizziness, fever, flushing, hemolysis, headache, hypertension, hypotension, meningismus, myalgia, nausea, photophobia, skin rash, tachycardia, vertigo, and vomiting. In acute ITP patients, these events were generally reported as mild to moderate in severity. In chronic ITP patients, these events were sometimes categorized as severe. Adverse events were generally transient (from three to 48 hours after the infusion ceased) and controlled with therapeutic agents such as anti-emetics or oral non-narcotic analgesics if these were needed. Adverse events that were classified as more serious or severe included acute renal failure, anaphylaxis, aseptic meningitis, convulsions, seizures, and sepsis. Some adverse events were so severe that they resulted in a lengthened hospital stay or the discontinuation of therapy. The dosage and duration of IVIg administration generally affected the incidence of adverse events; lower doses over longer durations tended to result in fewer adverse events. One study⁸¹ found that children younger than 5 years of age “appeared less likely to have AEs with any dosage regimen.”

b) Rationale for product use

Half of the studies communicated the need for a rationale regarding IVIg use or the standardization of IVIg use.^{23-25,44,53,62-66,70,72,73,75,79} The key factors regarding IVIg use in acute ITP were “the assumption that a rapid reversal of thrombocytopenia will minimize the risk of intracranial hemorrhage and other severe bleeding...[and] the anxieties of parents and physician about the risk of bleeding,”⁶² despite the widespread acknowledgment that “the risk of life-threatening bleeding, such as intracranial hemorrhage, is quite low in acute ITP, even in patients who are severely thrombocytopenic.”⁶³ Benesch et al.'s statement that the “lack of trials evaluating the true clinical benefit of different therapeutic strategies (rather than the treatment-related rise in platelet counts) has made the appropriate therapeutic management of acute ITP a matter of debate for nearly half a century”⁶⁴ was in concordance with others.^{24,44,65,66,73} Regarding chronic ITP, Hollenberg et al.²³ stated that “in actual practice, several families, particularly those with affected adolescents, have found the protracted course of IVIg therapy intolerable and opted for early splenectomy despite the risks of operative fatality or sepsis. Other families have refused to consider splenectomy because of its risks and opted for the IVIg strategy.”²⁵

c) Cost

Nine trials^{47,53,62,63,70-72,77,79} noted that IVIg therapy is expensive or more costly than the use of study comparators or alternative therapeutic agents. One study's authors questioned the justification for the use of IVIg in light of its expense,⁶³ with another advocating the restriction of the use of IVIg in "extreme emergency cases and in patients with infection"⁷⁰ due to its expense. Other authors suggested that methods of IVIg therapy cost reduction should be considered in future research.^{69,79} IVIg dose reduction was proposed as a potential solution to offset the cost of therapy in the treatment of patients with ITP.⁷⁹

Regarding the issue of IVIg expense, Blanchette et al. observed that "for the majority of children (who are young and therefore small) it is not prohibitively expensive."⁶⁵

The issue of IVIg cost was discussed in all four economic evaluations.²³⁻²⁶

d) Product safety

Many studies focused on IVIg's biologic or plasma-derived product status.^{23,46,49,62,63,65-67,69,70,79} Exposure to IVIg was cited as having the potential to transmit viruses to users^{49,63,70} and a cause of fear and concern by potential study participants and patients' families.^{65,66} Wolf et al. cautioned that "despite the high safety record of IVIG with regard to blood-borne infectious agents, pathogen transmission cannot be totally excluded, as some non-enveloped viruses and transmissible spongiform encephalopathy agents resist current inactivation techniques."⁴⁹

The generally positive safety record of many IVIg products was acknowledged,^{23,63,79} with some studies outlining the processes used to ensure the safety of specific products.^{46,49,67} Three studies tracked patients' viral markers with results remaining negative regarding viral status.^{49,67,69}

e) Product administration

Two studies observed that IVIg requires intravenous infusion,^{62,63} which generally lasts several hours.

f) Product supply and manufacture

The limited IVIg supply was mentioned.⁶³ The fact that there are different product manufacturers, which might have implications for product comparability, was noted by Godeau et al.⁵³

g) Patient quality of life

Patient quality of life was rarely mentioned in the studies that we examined. O'Brien et al. commented on the paucity of "research conducted on the impact of ITP in general on a child or parent's quality of life" and the lack of clarity regarding "whether quality of life is more negatively affected by the disease and the accompanying fear of hemorrhage, or by the toxicity, expense, and inconvenience of treatment."²⁵ Bussel et al. noted that "further studies examining the effects of IVIG infusion on quality of life...are warranted."⁶⁹

7.3.3 Discussion

The review of clinical and economic papers identified planning, implementation, utilization, equity, legal, regulatory, ethical, and psychosocial issues that could be more easily summarized by

their placement into naturally occurring categories. The most prevalent issues were adverse event incidence, rationale for IVIg use, product cost, and the possibility of blood-borne virus transmission.

The administration of any therapeutic agent when there are known side effects has ethical implications. Patients should be notified about the potential adverse effects before IVIg administration so that they may make an informed decision regarding their willingness to undergo therapy.

Rationalizing or making recommendations regarding IVIg use based on inconclusive scientific evidence has ethical implications for physicians, because the decision to treat or not to treat with IVIg can affect patients in different ways.

The cost of IVIg can be a barrier to patient access, depending on financial resources and the guidelines of the jurisdiction where the patient is being treated. This potential barrier to access may also have ethical, legal, and psychosocial implications. Denying a patient treatment based solely on cost can be perceived to be unethical and could also have legal implications should the patient suffer needlessly. The lack of treatment may result in avoidable patient anxiety or physical suffering.

Patients' concerns about the potential transmission of blood-borne viruses through IVIg have legal and ethical ramifications. Regulators are responsible for ensuring the safety of such products. Negligence can result in legal action against physicians or product providers. Patients and their representatives must be made aware of all safety issues before consenting to treatment with this product.

The issues of IVIg administration route, limited product supply, manufacturing variations, and patient quality of life were noted by authors. These issues should be considered when discussing the human and material resource needs for IVIg implementation.

The limited supply of IVIg requires consideration during planning to ensure that its distribution is fair and equitable.

Manufacturing variations in the formulation or purification processes, or variations that cause larger or smaller amounts of the resulting product, result in certain products being more clinically suited to certain populations, certain products having a greater likelihood of being more or less virus-free than others, or IVIg being more or less available for patients' use. These issues can lead to possible legal and ethical implications.

One clinical expert noted that our findings regarding the planning, implementation, utilization, equity, legal, regulatory, ethical, and psychosocial content in the studies that we reviewed reflected those issues that arise in primary practice. In particular, the issues of whether the amount of risk and expense of IVIg therapy are warranted in a given patient resonated with the clinician (Dr. Colin Chalk, Department of Neurology and Neurosurgery and Department of Anatomy and Cell Biology, McGill University, Montreal, PQ: personal communication, 2008 Apr).

After examining the review, a second clinical expert noted that the issue of the disparity between the existing Canadian regulations for IVIg use and reimbursement and the reality of IVIg's off-label use based on clinical or consensus opinion had not been mentioned (Dr. David Pi, B.C. Provincial Laboratory Coordinating Office, Vancouver, BC: personal communication, 2008 Apr).

8 CONCLUSIONS

The two primary economic evaluations conducted in this review indicate that the cost-effectiveness of IVIg for the treatment of ITP may differ according to the patient population being treated. In the analysis of treatments for acute childhood ITP, the base case incremental cost per QALY for IVIg was estimated to be \$56,000 compared to single-dose anti-D. Depending on structural assumptions (for example, dosing regimen, patient weight), the cost-effectiveness estimates varied. In the economic evaluation of IVIg for the treatment of chronic adult ITP, the cost-effectiveness of IVIg was found to be less favourable. In the base-case analysis, the incremental cost-effectiveness of IVIg compared with prednisone was estimated to be more than \$2 million per QALY. This high ICER associated with IVIg in chronic adult populations was mainly due to the small difference in initial response and long-term relapse rates between IVIg and prednisone.

The differences between the two cost-effectiveness model results are important given the potential impact of IVIg on health services in Canada. Based on published prevalence and incidence studies, the number of chronic adult cases of ITP in Canada was estimated to be larger than the number of acute childhood cases (6,090 versus 268). In addition, patients with chronic ITP may require long-term maintenance therapy. The annual average IVIg maintenance cost for chronic ITP was estimated to be \$25,935. In comparison, the average cost for acute management of childhood ITP was estimated to be \$1,539 in the health service impact analysis.

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APPENDICES

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