CANADIAN COST-UTILITY ANALYSIS OF INTRAVENOUS IMMUNOGLOBULIN FOR ACUTE CHILDHOOD IDIOPATHIC THROMBOCYTOPENIC PURPURA

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ABSTRACT

Background
Idiopathic thrombocytopenic purpura (ITP) is a hematological disorder and can be classified as acute or chronic. The main goal of treatment for acute childhood ITP is the prevention of potentially fatal bleeding complications, the most serious of which is intracranial hemorrhage (ICH). Treatment options for acute childhood ITP include splenectomy, corticosteroids, and blood products such as intravenous immunoglobulin.

Objectives
The objective was to evaluate, from a Canadian perspective, the cost-effectiveness of intravenous immunoglobulin (IVIG) compared to alternative inpatient treatments for acute childhood idiopathic thrombocytopenic purpura (ITP).

Methods
A Markov model with a lifelong time horizon was used to evaluate the costs and quality-adjusted life years (QALYs) for 5 treatments for children hospitalized for ITP: 1) no treatment; 2) IVIG; 3) Anti-D; 4) prednisone; and 5) methylprednisolone. The model predicted the probability of intracranial hemorrhage for each treatment strategy based on the time children spent with platelet counts <20,000µL. The time patients spent with platelet counts <20,000µL with each treatment was estimated by pooling data from published randomized clinical trials. In the basecase analysis, the cohort was assumed to weigh 20kg. Cost and utility model variables were based upon various literature sources. Parameter uncertainty was assessed using probabilistic sensitivity analysis.

Results
The treatment strategies that comprised the efficiency frontier were prednisone, Anti-D and IVIG. The incremental cost per QALY was $53,333 moving from prednisone to Anti-D and $53,846 moving from Anti-D to IVIG. Results were sensitive to patient weight. If patient weight is 10kg, IVIG dominates all other strategies and if weight is increased to 30kg, the cost per QALY of IVIG is $163,708.

Conclusion
Based on common willingness to pay thresholds, IVIG might be considered a cost effective treatment for acute childhood ITP. Cost effectiveness is highly dependent on patient weight.

Key Words: *Purpura; thrombocytopenic; idiopathic; cost benefit-economics; immunoglobulins; intravenous*

Idiopathic thrombocytopenic purpura (ITP) is one of the most common hematological disorders. ITP is classified as acute or chronic, with chronic being defined as the persistence of thrombocytopenia (platelet count <150,000/μL) for more than 6 months after initial presentation of symptoms.[1] The pathophysiologic mechanisms are postulated to differ between the two types of ITP. In acute ITP, platelet destruction arises from antibodies generated during the immune response to a viral or bacterial infection that cross-react with platelet antigens. Also, other mediators in the immune response may play a role in suppressing platelet production.[1] Chronic ITP may be a consequence of an inherent defect in immune regulation, as is seen in other autoimmune disorders resulting in the generation of platelet-specific antibodies.[1] Acute ITP is more prevalent in children younger than 10 years of age.[1] Children, previously healthy, usually present with a short history of mucocutaneous bleeding (e.g. bruising and petechiae) over a few days to weeks after an infectious viral illness, and have a very low platelet count (<20,000/μL). The disease usually resolves itself without treatment with a favourable prognosis in more than 70 - 90% of cases within six months. The main goal of treatment for acute childhood ITP is the prevention of serious and potentially fatal bleeding. Intracranial hemorrhage (ICH) is the most serious and life-threatening complication, which is most likely to occur when the platelet count is less than 20,000/μL.[2] The risk of ICH is estimated to be between 0.1% and 1% and occurs most often during the first 48 hours of onset.[2] There is a debate over the optimal management approaches for these children. Most children are managed on an outpatient basis, especially if there is no bleeding. Hospitalization is appropriate for platelet counts <20,000/μL and life threatening bleeds, mucous membrane bleeding or if the child is inaccessible or non-compliant.[3,4] Treatment options for ITP include splenectomy, corticosteroids, and blood products.

Blood products isolated from large volumes of human plasma by cold-ethanol fractionation include polyclonal intravenous immunoglobulin (IVIG),[5] and anti-D immune globulin.[6] IVIG contains all 5 mammalian antibody isotypes (IgA, IgD, IgE, IgG, IgM), but IgG is the major component. Anti-D immunoglobulin only contains the isotype IgD and since it targets the D antigen it will only be effective in persons who carry this antigen on their blood cells known as Rh positive blood type.

Canada's plasma supply comes from both voluntary donations within Canada and paid donors in the United States (U.S.).[3] Canada is one of the highest per capita users of IVIG along with the U.S.[7] The average yearly increase in IVIG utilization reported by Canadian Blood services from 1997 – 2008 is 11.3% , varying from 6.8% - 20.0%.[8] The cost of IVIG is $550 - $1100 per infusion of 0.5-1.0g/kg for a 20 kg child.[3]

Assessing the costs and effectiveness of IVIG in patients with ITP has been identified by the Canadian government as a priority, given its relatively high utilization rates in Canada, the potential availability of alternative treatments and an uncertainty of a therapeutic advantage over alternate therapies. The objective of this study is to evaluate, from a Canadian perspective, the cost effectiveness of IVIG compared to other inpatient treatments for acute childhood ITP.

METHODS

Overview

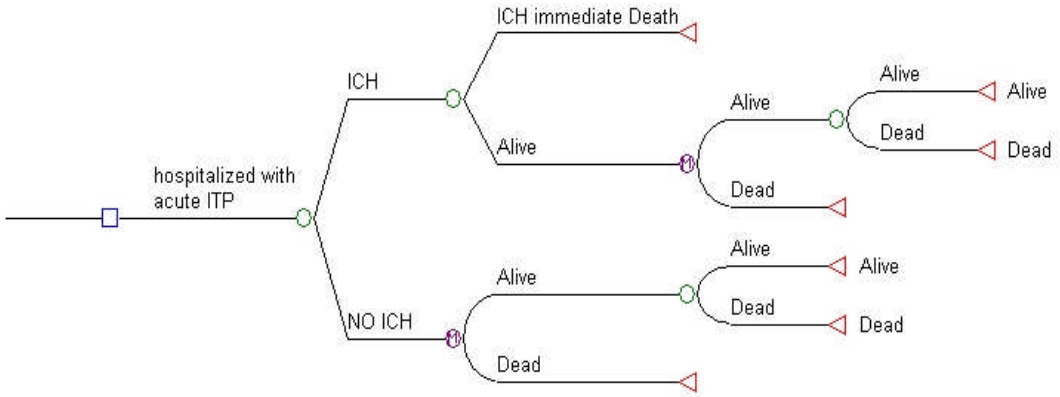
A Markov model was used to assess the lifetime cost-utility of 5 treatment strategies for acute childhood ITP. The treatment strategies considered were: 1) observation (no treatment); 2) IVIG (single dose 0.8 g/kg); 3) Anti-D (single dose 75 mcg/kg); 4) prednisone (4 mg/kg per day for 4 days); and 5) IV methylprednisolone (30 mg/kg for 3 days). These strategies were assumed in another published economic evaluation of treatment strategies for childhood ITP.[9] A haematologist confirmed that these dosing regimens were relevant in Canada. The population entering the model are hospitalized children with ITP and a platelet count <20,000/μL. The model cohort was assumed to be 6 year olds weighing 20kg. A starting age of 6 was chosen because this corresponds to the average age (5.7 years) of patients in a large published childhood ITP registry.[10] The weight of 20kg was based on the assumption used in Canadian IVIG treatment guidelines in their estimate of the cost of treating childhood ITP.[3] The analysis is performed from a third-party health care payer perspective. A lifelong time horizon is used in the model and

both costs and outcomes were discounted at 5% annually. The outcome of the economic analysis is the incremental cost per quality adjusted life year (QALY) gained. The QALY was chosen as the outcome because it allows for the incorporation of both mortality and morbidity over time. The incremental cost per QALY is a common measure in economic evaluations. This makes it easier to compare the incremental cost-effectiveness findings to those found in other evaluations.

Model Structure

Figure 1 presents the structure of the model. The model begins with children who are hospitalized due to an increased risk of ICH, which is associated with platelet counts <20,000/μL. The model assumes that all patients, including those who are just observed, are hospitalized until platelet counts reach safe levels. A per diem hospital cost is assigned to the length of the hospitalization. For each treatment group there is a risk of an ICH. The probability of ICH for each strategy depends on the amount of time patients spend with platelet counts <20,000/μL. Patients who have an ICH during their hospital stay are at risk of immediate death. Patients who have an ICH are assigned the additional cost of an ICH hospitalization. Patients, who do not die from an ICH during the acute episode, enter the Markov model which has a cycle length of 1 year. The Markov model essentially has a lifelong time horizon, as it is run until all patients die or reach the age of 110. The lifelong time horizon allows the model to capture the long term mortality and quality of life impact of an ICH. Patients are at risk of death during each 1 year cycle. Age-specific utility values are applied to the patients who were alive in each year of the Markov model. This allows for patients to accrue QALYs during the long term model phase. Patients who experience an ICH during the acute ITP episode but survive, are assigned a lower utility value and additional health care costs in each cycle.

FIG. 1



Model Input Parameters

Various clinical, cost, mortality and utility input parameters were used to populate the model. None of the trials reviewed used a bleeding end-point; therefore, an intermediate endpoint was used, which is the platelet count. The main clinical effectiveness input variable in the model is the mean time patients, in each treatment group, spent with platelet counts <20,000/μL. This was estimated using data from clinical trials identified in a recent systematic clinical review of IVIG in ITP[11] and from a supplemental literature search. Only studies with a baseline population of children with platelet counts <20,000/μL were included in the analysis. Only a few of the studies reported the mean time patients spent with platelet counts <20,000/μL. Most studies reported the proportion of patients achieving platelet counts

>20,000/μL at different points in time after treatment initiation. Data for each treatment was pooled regardless of dosing used in the trial. To estimate the time spent with platelet counts <20,000/μL, data on the proportion of patients with platelet counts >20,000/μL at 1 day, 2 days, 3 days, and 7 days after therapy initiation were pooled by treatment group. Supplemental Table 1 provides details on the studies and data included in the pooled analysis. The age range of participants in these nine trials is large, varying from 6 months to 17.4 years and sample sizes are small; 2 to 42 patients per treatment arm. Only two studies used an observation only arm.[12,13] All treatments were randomized except in one study[13] where parents had to consent to the no treatment arm. If consent was not given, the child was randomized to one of the treatment arms. Follow-up duration also varied across the studies: 1 month,[13,14] 3 months,[15] 6 months[12,16,17] and 12 months.[17-19] Newman et al.[20] is a brief report and they do not specify age of participants or follow-up time period. Data was pooled by day for each treatment using a random effects meta-analysis.[21] Using the proportion of patients with platelet counts >20,000/μL at the different time points, a "time to platelet count >20,000/μL curve" was constructed for each treatment. Based on these curves, the time spent with platelet counts <20,000/μL was estimated for each treatment. The other key clinical variable in the model is the probability of an ICH when platelet counts are <20,000/μL, which was based on data from Lilleyman et al.[22,23]

The unit cost of IVIG and Anti-D was provided by Canadian Blood Services and represents prices for fiscal 2008/2009 (Mathias Haun, Director, Plasma Products and Services, Canadian Blood Services, Ottawa, ON: personal communication, 2008 Apr). The cost per pill of prednisone and for methylprednisolone 100mg/5ml suspension pack were derived from the Ontario Drug Benefit Formulary.[24] The cost per ITP hospitalization day and the cost for ICH hospitalization were based on data from the Ontario Case Costing Project.[25] The annual post-stroke costs were based on a recent Canadian longitudinal analysis of matched diabetic and non-diabetic patients.[26]

Age specific annual mortality rates were based on Canadian life tables.[27] The probability of immediate death following an ICH was based on findings from a prospective study of stroke outcomes in the U.K.[28] Age specific utility values used in the long-term phase of the model were based on a study that estimated utility values in the U.K. general population.[29] The post-ICH utility weight was based on the mean utility for major stroke reported in a study by Shin et al.[30]

TABLE 1

	n[a]	Day 1 proportion with platelets >20,000/μL (95% CI's)	n	Day 2 proportion with platelets >20,000/μL (95% CI's)	n	Day 3 proportion with platelets >20,000/μL (95% CI's)	n	Day 7 proportion with platelets >20,000/μL (95% CI's)	Days Platelets <20,000/μL
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
Methyl	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

Pooled estimates of the proportion of patients with platelet counts <20,000/μL by day and by treatment and time with platelet counts <20,000/μL
n[a] – number of studies, see Supplemental Table 1 for study details

RESULTS

Model Input Parameters

Table 1 provides pooled estimates of the proportion of patients with platelet counts <20,000/μL at day 1, 2, 3 and 7 for each treatment group. The upper and lower 95% confidence intervals (CI) for each estimate are also provided along with the number of arms that comprise each estimate. The last column includes the estimate of days spent with platelets <20,000/μL for each treatment. As shown, the mean number of days with platelet counts <20,000/μL is estimated to be 1.34 for IVIG, 1.83 for Anti-D, 2.10 for prednisone, 2.18 for methylprednisolone and 3.33 for no treatment (observation).

Table 2 provides a summary of the values for other model parameters. Based on a retrospective survey of all cases of an ICH in children with ITP in the U.K., Lilleyman estimated that an ICH occurs in 0.1% of all childhood ITP cases.[22] In a later publication, Lilleyman[23] stated that the probability of an ICH in the "first few days after diagnosis" is between 0.1-0.2%. This range was based on an estimate on the number of potential unreported cases of ICH in the 1994 Lilleyman study.[22] For the basecase model it was assumed that the probability of an ICH was 0.0375% (0.15%/4 days) for each day the platelet counts were <20,000/μL. This assumption was altered in the sensitivity analysis. The probability of immediate death following an ICH was assumed to be 50% (95% C.I. 38%-62%).The unit costs for the medications/blood products compared in the model are shown in Table 2. Based on our assumed dosing regimens, the cost of treatment with IVIG, Anti-D, prednisone and methylprednisolone for 20kg patients is estimated to be $947.04, $375.20, $0.73 and $189.18, respectively. The cost per ITP hospitalization day, cost per ICH hospitalization, and annual post-ICH costs used in the model were $892, $18,302 and $4,624, respectively. 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.

TABLE 2

Model Variable	**Base case Value**	**Distribution**	**95% CI based on distribution and parameters**
ICH Probabilities			
Probability of ICH When platelets<20,000/μL	0.000375	Beta	(0, 0.0017)
Probability of immediate death after ICH	0.50	Beta	(0.38, 0.62)
Cost variables			
IVIG per gram	$59.19	No distribution	
Anti D per 300 mcg vial	$75.04	No distribution	
Prednisone per 50mg Tab	$0.0913	No distribution	
Methylprednisolone per 100mg/5ml InjSusp-5mLPkp	$10.51	No distribution	
Cost per ITP hospital day	$892	Gamma	(532,1173)
Cost per ICH hospitalization	$18,302	Gamma	(13684, 23600)
Annual cost of ICH	$4,624	Gamma	(4453, 4794)
Utility weight post-ICH	0.45	Beta	(0.33, 0.56)

Uncertainty

Parameter uncertainty for the primary economic outcome in the basecase model was assessed using probabilistic sensitivity analysis. In probabilistic sensitivity 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 strategy can be calculated given a specified willingness to pay value. Beta distributions were assigned to model variables constrained to values between 0 and 1 (probabilities, utilities). Gamma distributions were assigned to model cost variables. Details of distributions used, and the 95% CI resulting from the distribution of parameters assigned, are provided in Tables 1 and 2.

A number of 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 probabilistic analysis (daily probability of an ICH).

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BASECASE RESULTS

Basecase model results for the primary economic outcome are presented in Table 3. As shown, the strategy with the lowest expected costs is prednisone ($1,844). The strategy with the highest expected costs is observation ($2,820), and IVIG has the 2nd highest expected costs in the basecase analysis ($2,080). Different categories of costs are presented in Table 3. These are costs of treatment (medications and blood products), hospital costs during acute treatment and costs deriving from cases of ICH (short term and long term). As shown, IVIG was associated with the highest treatment cost ($947) amongst the 5 strategies however 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 <20,000/μL, leading to the shortest time in hospital.

TABLE 3

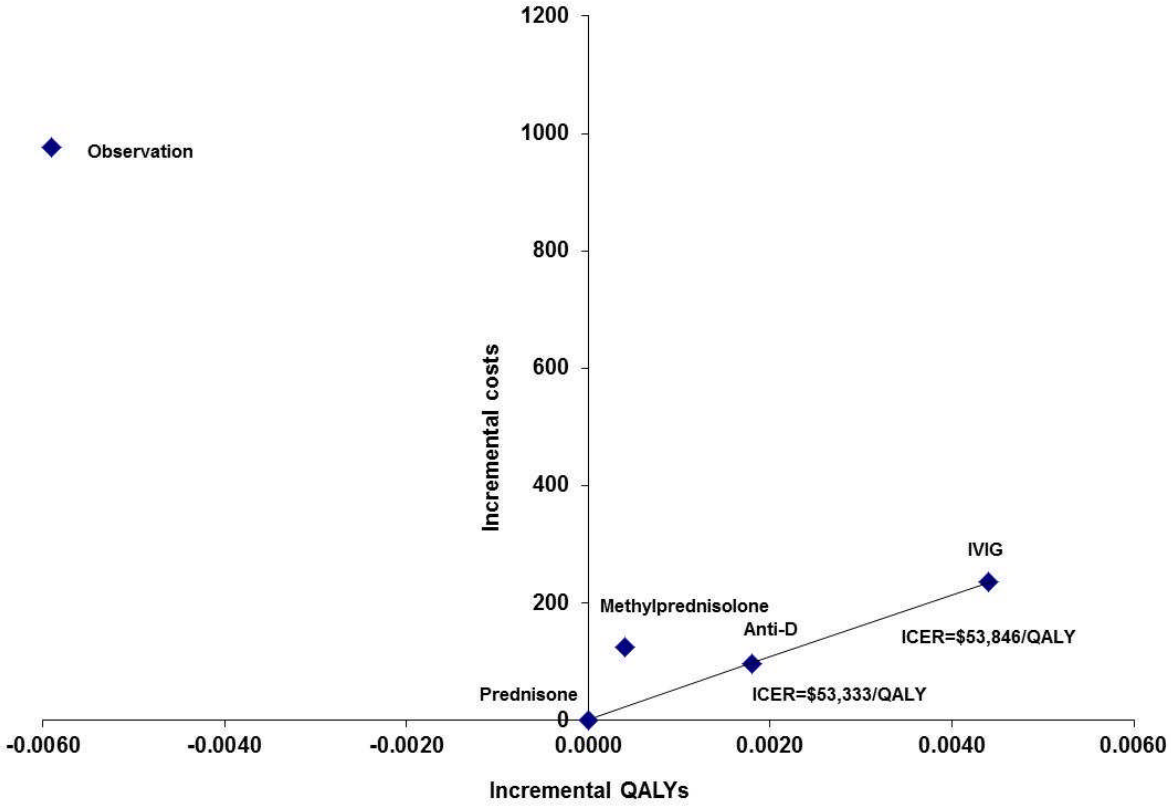
	Treat	Hospital	ICH	Total		---------Incremental---------		
Treat	Costs	Costs	Costs	Costs	QALY's	Costs	QALY's	ICUR
Pred.	$1	$1,790	$53	$1,844	17.6915	Ref.	Ref.	Ref.
Methyl.	$189	$1,729	$51	$1,969	17.6919	$125	0.0004	Dom.
Anti-D	$375	$1,521	$44	$1,940	17.6933	$96	0.0018	$53,333[1]
IVIG	$947	$1,100	$32	$2,080	17.6959	$236	0.0044	$53,846[2]
Obs.	$0	$2,739	$81	$2,820	17.6856	$976	-0.0059	Dom.

Expected lifetime costs, QALYs and incremental costs, QALYs and Cost/QALY gained Pred=Prednisone, Methyl=Methylprednisolone, Obs=Observation, Ref.=reference, Dom.=Dominated
[1]Relative to prednisone
[2]Relative to Anti-D

The observation strategy has the lowest expected QALYs (17.6856) while IVIG has the highest expected QALYs (17.6959). This is to be expected since these two strategies have the highest and lowest time with platelet counts <20,000/μL and therefore, the highest and lowest likelihood of incurring an ICH amongst the 5 strategies.

To determine the incremental cost-utility, the strategies that make up the cost-utility efficiency frontier must be determined. The first step is to identify strategies that are either strictly dominated or extendedly dominated by other strategies. A treatment strategy is strictly dominated if it has both higher costs and fewer QALYs than at least one other strategy. A treatment strategy is considered to be extendedly dominated if it results in higher costs and fewer QALYs compared to a combination of two other strategies. Non dominated strategies make up the cost-utility efficiency frontier. Starting from the least costly strategy, incremental cost-utility ratios (ICUR) are calculated moving from one strategy on the frontier to the next. The cost-utility efficiency frontier is provided in Figure 2.

FIG. 2



As shown in Figure 2, the observation treatment strategy is dominated by all other strategies. The methylprednisolone strategy is extendedly dominated by the Anti-D strategy, meaning Anti-D therapy provides more QALYs and is less costly then 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 $53,846. This means that based on these results, IVIG can be considered a cost-effective strategy if a decision makers' willingness to pay for a QALY is equal to or greater than $53,846. Furthermore, prednisone can be considered a cost-effective strategy if a decision makers' willingness to pay for a QALY

is less than $53,333. If the willingness to pay threshold is between $53,333 and $53,846, then treatment with Anti-D can be considered the cost-effective strategy.

Sensitivity Analysis

Based upon the probabilistic sensitivity analysis the prednisone strategy has the highest probability of being cost-effective up to a willingness to pay value of $112,000 per QALY. IVIG has the highest probability of being cost-effective at ceiling ratios greater than $112,000. Cost effectiveness acceptability curves for the five strategies are provided in Figure 3. A number of one-way sensitivity analyses were conducted on model parameters and assumptions made in the primary analysis and the results are presented in Table 4. Because the observation and methylprednisolone strategies were dominated in all sensitivity analyses, their results are not provided. Changing the discount rate from 5% to 3%, the ICUR of Anti-D compared to prednisone becomes $34,703 per QALY and the ICUR of IVIG compared to Anti-D becomes $36,071. Changing the discount rate to 0% substantially decreases the ICUR for both strategies.

FIG. 3

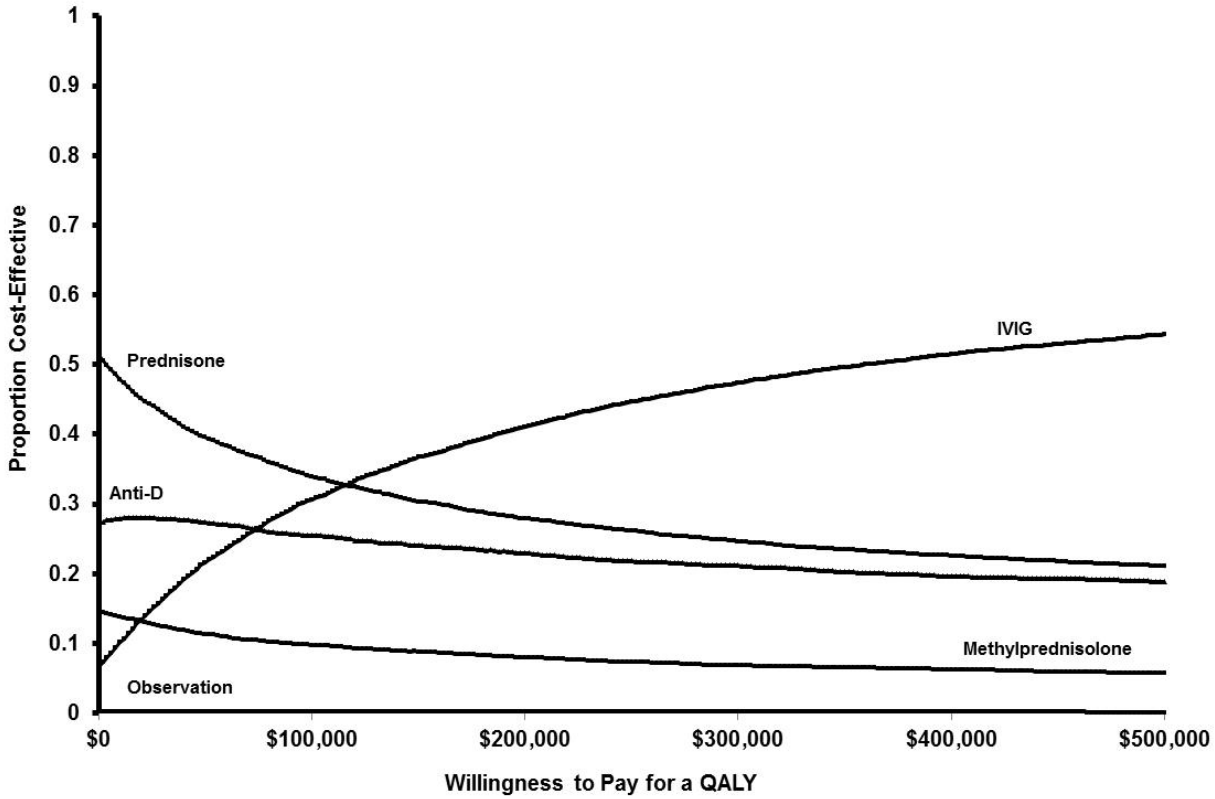


TABLE 4

	$/QALY		
	Prednisone	**Anti-D**	**IVIG**
Base case	reference	$53,333	$53,846
Discount rate			
0%	reference	$12,411	$12,979
3%	reference	$34,703	$36,071
IVIG dosing			
1g/kg	reference	$53,333	$150,664
Probability of ICH per day			
0.0001	reference	$212,765	$220,398
0.0005	reference	$38,793	$40,319
0.001	reference	$17,046	$17,810
Weight of Child			
10kg	dominated	dominated	dominates
20kg	reference	$53,333	$53,846
30kg	reference	dominated	$163,708
40kg	reference	$260,747	$281,648
50kg	reference	dominated	$382,253

Assuming different dosing regimens for IVIG has a large impact on the results. Recent Canadian based IVIG guidelines[3] suggested that a single dose of IVIG 0.8g to 1g/kg is appropriate for acute childhood ITP, with a second dose given if platelet levels are not >20,000/μL. If the IVIG dosing is changed from 0.8g/kg to 1g/kg, the ICUR moving from Anti-D to IVIG rises to $150,664 per QALY. Assuming different daily probabilities of ICH when platelet counts are <20,000/μL also affects the results. As the per day probability of ICH decreases, the cost per QALY of Anti-D and IVIG begin to rise until the cost per QALY exceeds $220,000. As the assumed weight of the cohort rises, the cost per QALY also rises so that the incremental cost per QALY of IVIG for a 50kg child becomes $382,253.

DISCUSSION

In this Canadian economic model evaluating treatments for acute childhood ITP, the incremental cost-utility ratio of Anti-D compared to prednisone treatment was estimated to be $53,333 per QALY; and $53,846 per QALY when moving to IVIG therapy. Therefore, if society's willingness to pay for a QALY is $53,836 or higher, IVIG can be considered a cost-effective treatment strategy for treating hospitalized 20kg children with acute ITP. These results differ from the cost-utility estimates from a recent U.S. economic evaluation of acute ITP treatment strategies. O'Brien et al.[31] estimated the incremental cost-utility of Anti-D compared to prednisone to be $7,616 per quality adjusted life day. This is the equivalent of $2,779,840 per QALY. Their analysis found IVIG to be

dominated by Anti-D (more costs, less effective). One of the main reasons for the different findings is that the time horizon was limited to the acute hospitalization episode. However, this assumption does not fully capture the long term impact of an ICH. A child with ITP suffering a fatal ICH during an acute episode will lose many years of life. A child surviving an ICH may have reduced quality of life for the remainder of their life. This is not captured if the time horizon is limited to the duration of the acute episode. Our model uses a life time horizon, allowing for the long term mortality and quality of life impact of ICH to be taken into account. Although using a lifetime model based on short term outcomes requires assumptions about unobserved long term outcomes, we felt that a long term horizon was needed to properly capture the long term effects of ICH.

The cost-effectiveness results were highly dependent on the probability of ICH as a function of the number of days patients have platelet counts <20,000/μL. In the model by O'Brien et al,[31] per day probability of ICH was assumed to be 0.1% based on data presented by Lilleyman et al.[22] However, this may be an overestimation of the per day ICH probability because this figure 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 <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 1-2%.[23] As shown in our sensitivity analysis, when higher rates of ICH are assumed, the cost-effectiveness of IVIG becomes more favorable.

There are a number of limitations to this study. One of the main limitations is the lack of direct evidence that treatment with IVIG leads to fewer ICH compared to alternate 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. That said, one of the roles of economic modelling is to take intermediate outcomes such as time with platelet counts <20,000/μL and estimate how that would translate into final outcomes such as ICH. Sensitivity analysis revealed that cost-effectiveness of IVIG varied by patient weight. There is an obvious correlation between children's weight and age. A limitation of this sensitivity analysis was that it assumed that older, heavier children would respond to treatment the same as younger, lighter children.

Some clinicians may use high-dose pulse dexamethasone instead of prednisone. High dose dexamethasone was not included in the model due to lack of published clinical effectiveness data in treating acute ITP. Additionally, the model did not include thrombopoeitin receptor agonist as a comparator. This was because no studies that included time to reaching >20,000ul platelets as an outcome were identified. IVIG is a relatively costly treatment used in a number of clinical indications. Physicians may be less aware of the cost of IVIG compared to pharmaceutical treatments. This is because IVIG is purchased as lump sum by Canadian Blood Services and do not appear as an individual line item in hospital formularies. Therefore it may be less obvious to physicians whether IVIG treatment is good value for money. This study provides evidence that IVIG is cost-effective for the treatment of children with ITP.

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Supplemental Table

study	Treatment	n	Day 1 Platelets >20,000	%	n	Day2 Platelets >20,000	%	N	Day3 Platelets >20,000	%	n	Day7 Platelets >20,000	%
Newman[20]	Anti D 75	8	6	75.00%									
Blanchette 94[19]	Anti-D 50	38	10	26.32%	38	27	71.05%	38	31	81.58%	38	34	89.47%
Tarantino[17]	Anti-D 50	35	17	48.00%							35	31	89.00%
Tarantino[17]	Anti-D 75	35	25	73.00%							35	33.6	96.00%
Moser[15]	Anti-D 75	25	19	76.00%									
Duru[13]	IVIG				12	8	67.00%	12	11	92.00%	12	11	92.00%
Erurden[16]	IVIG				22	19	86.36%				22	21	95.00%
Tarantino[17]	IVIG	35	27	77.00%							35	32	90.00%
Blanchette 94[19]	IVIG 0.8 g/kg	35	24	68.57%	35	31	88.57%	35	34	97.14%	35	34	97.14%
Ancona[14]	IVIG 1g/kg	42	23	55.00%	42	30	71.00%	42	40	95.00%			
Benesch[18]	IVIG 1g/kg							17	15	88.20%			
Blanchette 93[12]	IVIG 1g/kg	19	11	57.89%	19	18	94.74%	19	18	94.74%	19	18	94.74%
Blanchette 94[19]	IVIG1g/kg	34	13	38.24%	34	29	85.29%	34	32	94.12%	34	32	94.12%
Erurden[16]	Meth Oral				20	10	50.00%				20	19	95.00%
Ancona[14]	Methyl 1g/kg	35	13	37.00%	35	20	57.00%	35	26	74.00%			
Duru[13]	Methyl Oral				12	8	67.00%	12	11	92.00%	12	11	92.00%
Duru[13]	No therapy				26	11	42.00%	26	21	81.00%	26	23	88.00%
Blanchette 94[19]	No therapy	15	2	13.33%	15	3	20.00%	15	7	46.67%	15	10	66.67%
Blanchette 94[19]	Prednisone	39	12	30.77%	39	28	71.79%	39	31	79.49%	39	36	92.31%
Blanchette 93[12]	Prednisone	18	6	33.33%	18	12	66.67%	18	15	83.33%	18	17	94.44%

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