Appropriateness of the use of intravenous immune globulin before and after the introduction of a utilization control program

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ABSTRACT

Background: Intravenous immune globulin (IVIG) is an expensive and sometimes scarce blood product that carries some risk. It may often be used inappropriately. We evaluated the appropriateness of IVIG use before and after the introduction of an utilization control program to reduce inappropriate use.

Methods: We used the RAND/UCLA Appropriateness Method to measure the appropriateness of IVIG use in the province of British Columbia (BC) in 2001 and 2003, before and after the introduction of a utilization control program designed to reduce inappropriate use. For comparison, we measured the appropriateness of use during the same periods in the province of Alberta, which had no control program.

Results: Of 2256 instances of IVIG use, 54.1% were deemed to be appropriate, 17.4% were of uncertain benefit, and 28.5% were deemed inappropriate. The frequency of inappropriate use in BC after the introduction of the utilization control program did not differ significantly from the frequency before the program or the frequency in Alberta.

Interpretation: Almost half of IVIG use in BC and Alberta was judged to be inappropriate or of uncertain benefit, and the frequency of inappropriate use did not decrease after implementation of a utilization control program in BC. More effective utilization controls are necessary to prevent wasted resources and unnecessary risk to patients.

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➢ **Intravenous immune globulin (IVIG),** a fractionated blood product extracted from pooled human plasma from blood donations, is given intravenously to treat primary immune deficiency diseases and a wide array of autoimmune diseases, infections and other conditions. For some conditions, IVIG has been shown to be efficacious in randomized controlled trials, but often the evidence of benefit is less rigorous, with just case reports or uncontrolled case series suggesting benefit.[1–8] Many of these conditions without evidence of efficacy are frequently treated with IVIG, which may not always be appropriate. Even in diseases where efficacy has been shown, appropriate use will depend on the stage and severity of the condition and perhaps other factors.

Inappropriate use of IVIG exposes patients to unnecessary risks from adverse reactions[9] and increases health care expenditures because of the high cost of IVIG. IVIG use in Canada more than quadrupled in the 1990s,[10] and a typical course of IVIG (2 g/kg) for acute treatment currently costs more than Can$10 000. Also

of concern is the marked regional disparity in IVIG use. In 2001/02, the province of British Columbia (BC) used 0.07 g of IVIG per capita, whereas the province of Alberta used 0.12 g per capita.[11] Such marked variation suggests the possibility of either overuse (inappropriate use) or underuse.[12,13]

Concerns about inappropriate use prompted BC to introduce the IVIG Management Program in 2002. This province-wide program involved the provision of a handbook on IVIG utilization management with guidelines for prescribers, and a more specific request form intended to reduce inappropriate use.[10] Alberta, in contrast, did not undertake any concerted program to manage IVIG use. We used this "natural experiment" to formally assess the appropriateness of IVIG use in BC and Alberta and the effectiveness of BC's program.

Methods

The protocol was approved by the University of Alberta Health Research Ethics Board. Appropriate ethics approval and permission to review patient charts were obtained from each hospital and from individual physicians, when necessary.

Appropriateness ratings. We developed appropriateness criteria using the RAND/UCLA Appropriateness Method, a process that has been widely used to assess the appropriateness of health care interventions.[13,14] This method uses the best published literature for the use of the "product" under study. Because this evidence is often incomplete and insufficient on its own to make informed therapeutic decisions, it is combined with expert clinical opinion to arrive at balanced appropriateness ratings for the various scenarios under which the intervention might be used.

We performed a comprehensive review of the literature, and analyzed and summarized the evidence for the efficacy and effectiveness of IVIG in all medical conditions. We prepared a comprehensive set of clinical scenarios, each representing clinical circumstances under which IVIG might be used. The stage and severity of the diseases targeted by IVIG treatment were taken into account, as were other clinical factors that may influence treatment decisions.

An expert panel comprising specialists nominated by various Canadian national specialty societies was then convened. It included an immunologist, two hematologists (adult and pediatric), a neuromuscular neurologist, an obstetrician, a rheumatologist, an infectious disease specialist, a transfusion expert, a dermatologist and a general internist. The literature review and complete list of scenarios were reviewed by the panel and then revised. The panelists individually rated each scenario, based on the evidence and their experience, on a 9-point scale, where 1–3 represented an inappropriate indication for IVIG, 4–6 an indication for which IVIG use was of uncertain benefit and 7–9 an appropriate indication. The panelists then met under the chairmanship of a general internist/health services researcher (W.A.G.). During discussion of the scenarios, they made revisions and collapsed the initial set of 480 scenarios down to 326. Each scenario was then discussed and rated again, with no obligation for consensus.

The median ratings for each scenario were then applied to cases during a review of patient charts to determine the level of appropriateness of IVIG use. Following the chart reviews, we noted that some cases (3.5% of incident cases) did not correspond to any of the scenarios. We then developed 15 new scenarios to account for these cases, reviewed and summarized the relevant liberature and had the panel rate the new scenarios electonically. This left a total of 341 scenarios.

Cases and chart reviews. All patients who received IVIG in BC or Alberta in 2001 and 2003 were identified through lists kept by the BC Provincial Blood Coordinating Office and, in Alberta, by the blood banks of the individual hospitals. Lists of hospitals using IVIG in Alberta outside the 2 major centres (Calgary and Edmonton) were obtained from the Canadian Blood Services. An electronic chart abstraction database was constructed for the clinical data, incorporating all variables identified as necessary to categorize the cases by scenario, including diagnosis and stage or severity of disease. Research assistants abstracting the clinical data were trained to review the patient charts and enter the data directly into the database using laptop computers. Information about demographics, complications, dates of initial and subsequent treatments, dose and duration of treatment were also collected. Information was collected from hospital and outpatient clinic charts and physicians' office charts when necessary. Names and provincial health numbers were removed as soon as the full dataset was compiled. Appropriate privacy and security measures were taken, including full encryption of data.

Patient cases were divided into 2 categories on the basis of their clinical profiles: (1) incident cases (patients who received IVIG treatment for the first time in 2001 or 2003); and (2) continuing chronic cases (patients who started treatment before 2001 or in 2002 and therefore were not considered incident cases in either 2001 or 2003). For our study, we included only cases in the first

category, because we focused our analysis on the appropriateness of new therapeutic decisions to give IVIG.

Analysis. Using the clinical information collected from the chart reviews, we rated the appropriateness of IVIG use in each case. A computerized algorithm mapped each of the cases to one of the previously rated scenarios. Each case was then assigned to one of the three appropriateness categories: "appropriate," "inappropriate" and "uncertain."

Data analysis and presentation were primarily descriptive, with an overall reporting of the appropriateness of IVIG use, followed by a breakdown of appropriateness by main clinical indication (e.g., hematologic indications v. dermatologic v. immunologic v. other). Because the utilization control program was implemented in BC and not in Alberta, we performed a direct comparison of the appropriateness of IVIG use in the 2 provinces using the χ^2 test. In addition, we used logistic regression analysis to compare the appropriateness of IVIG use between the provinces while controlling for patient age, sex, clinical diagnosis and hospital teaching status.

To ensure a high level of interrater reliability, 80 charts were reviewed independently by both of the research assistants performing the data abstraction and were assigned appropriateness ratings using the algorithm as described above. The Kappa statistic for these dually reviewed charts was 0.65, which indicated substantial agreement.[15]

Results

Categorization and rating of clinical scenarios. Of the 341 unique scenarios covering the indications for which IVIG might be used, 77 (22.5%) were rated as appropriate (Table 1). Details of the scenarios and their ratings are available in the Excel file "IVIG Scenarios and Rating," available at www.imecchi.org/IMECCHI/OurProjects.aspx).

Description and rating of the clinical cases. In 2001 and 2003, there were 958 incident cases of IVIG use in Alberta and 1298 in BC, for corresponding rates of 34 per 100 000 and 33 per 100 000 (we used Canadian census figures for the population of each province to create a mean population base for each province for the 2 study years).

The cases from the two provinces were similar except that there were significantly more patients older than 65 years old in BC and fewer in teaching hospitals. There was a modest increase in the number of cases in each province in 2003 versus 2001. The most common indications for IVIG use were in the diagnostic categories of hematology (32.2%), neurology (17.6%), infectious disease (14.2%) and rheumatology (13.8%) (Table 2).

Overall, 54.1% of the cases were judged to be appropriate, 17.4% were of uncertain benefit and 28.5% were inappropriate (Table 3). The highest proportion of inappropriate cases was found in transplant care (80.8%), hematology (40.3%), obstetrics and gynecology (38.7%) and infectious diseases (24.6%). In the transplant category, the leading scenario in which IVIG use was rated to be inappropriate was allogeneic bone marrow transplant from a sibling donor. In hematology, it was initial treatment of idiopathic thrombocytopenic purpura in an adult with a platelet count of more than 20 × 109/L and no life-threatening bleeding. In obstetrics and gynecology, the leading scenario was recurrent spontaneous abortion. In the category of infectious diseases, the leading scenario was prevention of infection in a patient with chronic lymphocytic leukemia who had low levels of IgG but no history of serious infection.

Comparison of appropriateness over time. In Alberta, 47.3% of cases in 2001 and 43.6% in 2003 were judged to be appropriate (Table 4). In BC, the corresponding proportions were 61.1% and 60.7%. There was no significant difference in appropriateness ratings over time in either province. In particular, the lack of improvement in BC between 2001 and 2003 indicates that the intervention, introduced in 2002, had no discernible early effect on the appropriateness of IVIG use.

Table 1: Number of scenarios developed for assessing the appropriateness of intravenous immune globulin (IVIG) use appropriateness, inappropriateness and uncertainty

	Rating of IVIG use; no. of scenarios			
Diagnostic category	Appropriate	Inappropriate	Uncertain	Total
Overall	77	136	128	341
Dermatology	5	19	20	44
Hematology	31	33	15	79
Infectious diseases	6	20	23	49
Neurology	21	18	30	69
Obstetrics / gynecology	2	5	2	9
Rheumatology	7	15	21	43
Transplantation	1	13	10	24
Immunology	4	0	1	5
Other	0	13	6	19

Table 2: Characteristics of new patients who received intravenous immune globulin

Characteristic	Alberta cases (N = 958) n (%)	British Columbia cases (N = 1298) n (%)	*p* value
Age, yr			< 0.01
≤ 6	185 (19.3)	230 (17.7)	
7–17	119 (12.4)	93 (7.2)	
18–34	114 (11.9)	131 (10.1)	
35–64	343 (35.8)	494 (38.1)	
≥ 65	197 (20.6)	350 (27.0)	
Sex			0.46
Female	439 (45.8)	615 (47.4)	
Male	519 (54.2)	683 (52.6)	
Teaching hospital			< 0.01
No	127 (13.3)	645 (49.7)	
Yes	831 (86.7)	653 (50.3)	
Diagnostic category			< 0.01
Dermatology	21 (2.2)	23 (1.8)	
Hematology	288 (30.1)	441 (34.0)	
Infectious diseases	120 (12.5)	201 (15.5)	
Neurology	165 (17.2)	233 (18.0)	
Obstetrics / gynecology	16 (1.7)	15 (1.2)	
Rheumatology	123 (12.8)	189 (14.6)	
Transplantation	129 (13.5)	53 (4.1)	
Immunology	39 (4.1)	91 (7.0)	
Miscellaneous	14 (1.5)	10 (0.8)	
Missing	43 (4.5)	42 (3.2)	
Year			0.63
2001	467 (48.7)	646 (49.8)	
2003	491 (51.3)	652 (50.2)	

Table 3: Appropriateness of intravenous immune globulin use in new patients, by diagnostic category

		Rating of IVIG use; no. (%) of all cases			Inappropriate use by province; n (%) of cases		
Diagnostic category	Cases, n	Appropriate	Inappropriate	Uncertain	Alberta	British Columbia	*p* value
Overall	2256	1221 (54)	642 (29)	393 (17)	343	299	0.006
Dermatology	44	8 (18)	0	36 (82)	0	0	–
Hematology	729	397 (55)	294 (40)	38 (5)	144 (42)	150 (50)	0.038
Infectious diseases	321	113 (35)	79 (25)	129 (40)	33 (10)	46 (15)	0.027
Neurology	398	304 (76)	29 (7)	65 (16)	16 (5)	13 (4)	0.847
Obstetrics / gynecology	31	10 (32)	12 (39)	9 (29)	8 (2)	4 (1)	0.353
Rheumatology	312	261 (84)	15 (5)	36 (12)	6 (2)	9 (3)	0.292
Transplantation	182	10 (6)	147 (81)	25 (14)	98 (29)	49 (16)	0.001
Immunology	130	115 (89)	0	15 (12)	0	0	–
Miscellaneous	24	3 (13)	7 (29)	14 (58)	5 (1)	2 (1)	0.347
Missing	85	0	59 (69)	26 (31)	33 (10)	26 (9)	0.686

Discussion

We found that the frequency of inappropriate and uncertain use of IVIG was surprisingly high in Alberta and BC. The frequency of inappropriate use did not decrease significantly in BC after the introduction of the formal program of utilization controls, nor was it significantly lower than the frequency in Alberta, where there were no utilization controls.

This is not the first study to assess the pattern of IVIG use, its general appropriateness or the indications for use. Hanna and colleagues[16] described the pattern of IVIG use across Canada and the indications for use. They reported indications for use that were similar to those we have described. Their findings hint at a lack of uniform appropriateness, although they did not assess appropriateness using a formal method such as the one we used. Similarly, Lin and colleagues[17] and Hutchison and colleagues[18] assessed the use of IVIG in Australia and New Zealand, respectively. They found considerable interregional variation in utilization (this is typically a flag for both under- and over-utilization across jurisdictions[12,13]), and some questionable indications for use.

Our study extends these findings by using the more formal RAND/UCLA Appropriateness Method to study the appropriateness of IVIG use. That almost half of the cases of IVIG use were judged to be either inappropriate or of uncertain benefit is cause for concern. IVIG is an expensive and at times scarce blood product that confers substantial risk on its recipients.[9] Steps should be taken to reduce inappropriate use. As a first step, our methodologic template and scenarios can be applied by other jurisdictions interested in assessing IVIG use, and for this, the scenarios that we publish on the IMECCHI (International Methodology Consortium for Coded Health Information) website (www.imecchi.org/IMECCHI/OurProjects.aspx) constitute a methodologic tool for similar studies aimed at improving appropriateness.

Our findings raise questions about why BC's utilization control program failed to reduce inappropriate IVIG use. It is not surprising that the handbook and guidelines on IVIG use may not have influenced prescribing behaviour, given the abundant literature showing that clinical practice guidelines do not consistently change phyisician behaviour.[19,20] However, the apparent lack of effect of the special request form designed to reduce inappropriate orders for IVIG is surprising. A possible contributing factor to the program's lack of impact was that the baseline pattern of IVIG use in the province was already judged to be reasonably appropriate, but this alone does not fully explain the lack of effect. The persistence of inappropriate use of IVIG after implementation of the special request form suggests that orders for IVIG use in situations where use was inappropriate were not being blocked (otherwise, one would expect to have seen a precipitous drop in inappropriate IVIG use). Further, the form and the related utilization control program may have permitted some questionable use to proceed, because it may not have aligned fully with the indications that the RAND/UCLA Appropriateness Method identified as inappropriate.

Utilization controls in other clinical areas have had some positive effects. For example, Samore and colleagues[21] used a utilization control program that reduced inappropriate use of antibiotics in community practice settings. Bertakis and colleagues[22] developed a program that successfully targeted patients through education to reduce inappropriate use of health services. Constantine and colleagues[23] described a program in Atlantic Canada that may have slightly reduced the frequency of inappropriate use of IVIG; however, the evaluation of its effects was limited in its scope, and inappropriate use remained quite rampant despite the program's implementation in the mid-2000s. Targeted educational interventions can also have some effect in reducing inappropriate use, as has been shown in peri-surgical blood transfusion.[24]

Effective reduction of inappropriate IVIG use will require the development of more formal and vigorous utilization controls, with targeted educational interventions.

Table 4: Appropriateness of intravenous immune globulin use in new patients, by intervention group

Intervention group; rating of IVIG use	Year 2001* n (%)	Year 2003† n (%)	*p* value for appropriateness (year 2001 versus 2003) Crude	Risk-adjusted‡
Alberta (non-intervention province)				
Appropriate	221 (47.3)	214 (43.6)	0.93	0.70
Inappropriate	163 (34.9)	180 (36.7)		
Uncertain	83 (17.8)	97 (19.8)		
British Columbia (intervention province)				
Appropriate	392 (61.1)	394 (60.7)	0.42	0.31
Inappropriate	141 (22.0)	158 (24.3)		
Uncertain	113 (17.6)	100 (15.4)		

* Before intervention

† After intervention

‡ Adjusted for age, sex, teaching hospital and diagnosis category. (Adjusted and unadjusted *p* values < 0.01 for comparison of appropriate use between non-intervention and intervention group.)

Formal evaluation of the control program after its implementation will be required to ensure that it is reducing inappropriate use. The tools that we have developed for this study could be used for future evaluations of IVIG appropriateness in other jurisdictions.

Limitations. Our study has limitations. Most notably, our evaluation of the utilization control program in BC was merely an observational before–after study. The inclusion of IVIG use in Alberta for comparison strengthened the evaluation, but this approach still fell short of the inferences that could be drawn from a more definitive evaluation design such as a cluster randomized trial of utilization controls. Second, some years have passed since implementation of the program in BC. We intentionally focused our assessment around the years of the program's implementation, but there is now a clear need for continued assessment of IVIG use in more recent years. Third, our findings do not explain why the program had no effect. Physician interviews or surveys are one method that could be used to explore the underlying reasons. Fourth, we did not examine outcomes. We thus do not have evidence of ineffectiveness or harm in cases of inappropriate use, although this may be inferred. Finally, our appropriateness ratings were based in part on a comprehensive review of the IVIG literature rather than on a more rigorous systematic review.

Summary

Almost half of the instances of IVIG use in BC and Alberta were judged to be inappropriate or of uncertain benefit and that the frequency of inappropriate use did not decrease after implementation of a utilization control program in BC. These findings indicate that the use of this expensive product of limited availability requires continued monitoring through repeated appropriateness evaluations, and that jurisdictions need to consider the implementation and evaluation of more vigorous utilization control programs.

More broadly, high levels of inappropriate use have been found for many therapeutic and diagnostic health care interventions in many jurisdictions.[25] Reduction of inappropriate use could improve health outcomes, reduce health care costs and improve access to care. This would require the systematic study of appropriateness across a wide array of health care interventions coupled with the prospective implementation of appropriateness-informed utilization controls.[25]

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