**Utilization Controls and the Appropriateness of Intravenous Immunoglobulin**

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Thomas E Feasby designed the study and wrote the grant application, participated in the analysis of the data, drafted the manuscript and approved the final version.

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**ABSTRACT**

**Background:**

Intravenous immunoglobulin (IVIG) is an expensive and sometimes scarce blood product that carries some risk. It may often be used inappropriately. Educational interventions might reduce inappropriate use.

**Methods:**

We used the RAND-UCLA appropriateness method to examine the appropriateness of IVIG use in Alberta and British Columbia (BC). We measured appropriateness before and after the introduction of an intervention in BC designed to reduce inappropriate use.

**Results:**

Overall, 54.1% of 2256 cases of IVIG use were appropriate, 17.4% were of uncertain benefit and 28.5% were inappropriate. There was no improvement seen after the introduction of the BC IVIG utilization program.

**Interpretation:**

Almost half of IVIG use was either inappropriate or of uncertain benefit, causing wasted resources and unnecessary risk. Effective utilization controls are necessary and require more than an educational intervention.

**Introduction**

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 auto-immune diseases, infections and other conditions. For some conditions, the efficacy of IVIG has been demonstrated in randomized controlled trials, but often, the evidence of benefit is less rigorous with just case reports or uncontrolled case series suggesting benefit1-8. Many of these conditions without evidence of efficacy are treated frequently with IVIG and this may not always be appropriate. Even in diseases where efficacy has been shown, appropriate use will depend upon the stage and severity of the condition and perhaps other factors.

Inappropriate use exposes patients to unnecessary risks from IVIG adverse reactions9 and increases healthcare expenditures because of the high cost. IVIG use in Canada more than quadrupled in the 1990s10, and a typical course of IVIG (2 gm.kg) for acute treatment now costs more than $10,000. Also of concern, there is marked regional disparity in IVIG use. In two Canadian provinces in 2001-2, British Columbia (BC) used 0.07g of IVIG/capita while Alberta used 0.12 g/capita11. Such marked variation suggests the possibilities of either overuse (inappropriate use) or underuse12,13. Concerns about inappropriate use prompted BC to introduce a provincial IVIG Management Program in 2002 that included an IVIG Utilization Management Handbook with guidelines for prescribers, and a more specific request form in an attempt to reduce inappropriate use10. Alberta, in contrast, did not undertake any concerted program to manage IVIG use. We utilized this ‘natural experiment’ to formally assess the appropriateness of IVIG use in Alberta and BC and the effectiveness of the BC IVIG Management Program. We utilized the RAND/UCLA Appropriateness Method, a process that has been widely used to assess the appropriateness of healthcare interventions13,14.

**Methods**

The protocol was approved by the University of Alberta Health Research Ethics Board and appropriate ethics approval and permission to review patient charts was obtained from each hospital and from individual physicians, when necessary. The study was done in two Canadian provinces, Alberta and British Columbia.

1. ***Appropriateness Ratings***

Appropriateness criteria were developed using the RAND method13,14. A comprehensive review of the literature was done and the evidence for the efficacy and effectiveness of IVIG in all medical conditions was analyzed and summarized. A comprehensive set of clinical scenarios each representing clinical circumstances under which IVIG might be used was prepared, taking into account the stage and severity of the diseases targeted by IVIG treatment as well as 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 listing of scenarios (available to readers in a supplementary on-line appendix) 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 indicates an inappropriate indication for IVIG, 4-6 is uncertain and 7-9 is appropriate. The panel then met under the chairmanship of a general internist/health services researcher (WAG). During discussion of the scenarios, they made revisions and collapsed the initial set of 480 scenarios down to a total of 326. Each scenario was then discussed and rated again, with no obligation for consensus. The median ratings for each scenario were then ready to be applied to the cases to determine the level of appropriateness.

Following the chart reviews, we noted that some cases (3.5% of incident{new} 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 literature and had the panel rate the new scenarios electronically. This left a total of 341 scenarios.

***ii) Cases and Chart Reviews***

All patients receiving 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 the variables identified that were necessary to categorize the cases by scenario, including diagnosis and stage or severity of disease. Chart abstracters were trained to review the IVIG patient charts and enter the data directly into the database on 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 set was compiled. Appropriate privacy and security measures were taken including full encryption of data.

Patient cases were then divided into two categories based on their clinical profiles: 1) incident cases (first ever IVIG treatment received during 2001 or 2003); and 2) continuing chronic cases (chronic cases that started treatment before 2001 or in 2002 and therefore were not incident cases in either 2001 or 2003). The analysis in this study dealt with only the first category, as we focused on the appropriateness of *new* therapeutic decisions to give IVIG.

***iii) Analysis***

The clinical information collected in the chart review database was then used to rate each of the patients (i.e., clinical cases) receiving IVIG for their appropriateness of use. A computerized algorithm mapped each of the cases to one of the previously-rated case scenarios. Each IVIG 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 reporting by main clinical indication (e.g., hematological indications vs. dermatological vs. immunological vs. other). Lastly, given our interest in the ‘natural experiment’ associated with the IVIG utilization controls that exist in BC (and not in Alberta), we performed a direct comparison of the appropriateness of IVIG use in the two provinces, using chi-square tests. In addition, a logistic regression model was used to compare the appropriateness of IVIG use between provinces, while controlling for patient age, sex, clinical diagnosis, and hospital teaching status

To ensure a high level of inter-rater reliability, 80 charts were reviewed independently by both chart abstracters, and were assigned appropriateness ratings using the algorithm as described above. The Kappa statistic for these dually-reviewed charts was 0.65 for the three-level rating of appropriateness, indicating substantial agreement15.

**Results**

***i) Categorization and Rating of Clinical Scenarios***

We developed and rated 341 unique scenarios covering the indications under which IVIG might be used, 77 (22.5%) of which were rated as appropriate (Table 1). Details of the scenarios and their ratings are presented in a detailed on-line appendix (www.imecchi.org 16).

***ii) Description and Rating of the Clinical Cases***

There were 958 incident (ie new) cases who received IVIG in Alberta in 2001 and 2003 and 1298 who received IVIG in BC in the same years, for corresponding rates of 33/100,000 in Alberta and 34/100,000 in BC (using Canadian census figures for the population of each province to create a mean population base for each province for the 2 years to serve as the denominator).

The cases from the two provinces were similar except that there were significantly more over 65 years old in BC and fewer in teaching hospitals. There was a very modest increase in the number of cases in each province in 2003 versus 2001. The greatest utilization proportionally was for indications in the hematology (32.2%), neurology (17.6/%), infectious disease (14.2 (%) and rheumatology (13.8%) (Table 2)

Overall, 54.1% of 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 disease (24.6%). The leading scenarios rated to be inappropriate in each of these categories were: transplant (allogeneic bone marrow transplant from a sibling donor); hematology (initial treatment of idiopathic thrombocytopenic purpura (ITP) in adults, with a platelet count of >20,000 and no life-threatening bleeding) obstetrics (recurrent spontaneous abortion); infectious disease (infection prevention in patients with chronic lymphocytic leukemia (CLL), with low levels of IgG, but no history of serious infection).

***iii) Change in the Appropriateness over Time in the Two Provinces***

In Alberta, 47.3% of cases were appropriate in 2001 and 43.6% in 2003 (Table 4). In BC, 61.1% of cases were appropriate in 2001 and 60.7% in 2003. In both cases, there was no significant difference between the two years. In particular, the lack of a significant improvement in appropriateness in BC between 2001 and 2003 indicates that the BC IVIG Utilization Management Program, introduced in 2002, had no discernible early effect on the appropriateness of utilization.

**Discussion**

Our study shows that the RAND method can be applied to the complex task of assessing the appropriateness of IVIG utilization. Key findings are 1) that the method can be applied to IVIG use (and thus can be applied by other jurisdictions interested in formally studying IVIG utilization); 2) that the frequency of inappropriate (or uncertain) utilization is surprisingly high; and 3) that a formal program of utilization controls in BC was not associated with a reduction in inappropriate use of IVIG relative to both a pre-intervention period in British Columbia, or relative to the neighboring province of Alberta.

This is not the first study to assess the pattern of IVIG utilization, its general appropriateness, or the indications for use. Hanna et al17 described the pattern of utilization for IVIG across Canada, and the indications for use. Their findings generally resemble the indications for use that we describe in our study, and hint at a lack of uniform of appropriateness, though appropriateness was not assessed using a formal method such as we used. Similarly, Lin et al18 and Hutchison et al19 assessed utilization of IVIG in Australia and New Zealand, respectively, and demonstrated considerable inter-regional variation in utilization (that is usually a flag for there being both over- and under-utilization across jurisdictions12,13), and also some questionable indications for use.

Our study extends these findings by using the more formal RAND appropriateness method to study the utilization of IVIG. The finding that 46% of overall IVIG use was either inappropriate or of uncertain value is a striking cause for concern. This is an expensive, and at times, scarce blood product that confers significant risk on its recipients9. Steps should be taken to reduce inappropriate use. As a first step, our methodological template can be applied by other jurisdictions interested in assessing IVIG utilization, and for this, the scenarios that we publish in the accessible on-line appendix16 constitute a methodological tool for similar studies aimed at improving appropriateness.

We also provide unique information on a specific attempt to reduce inappropriate use, the IVIG utilization control program in British Columbia, with both baseline (pre-intervention) and post-intervention data for the jurisdiction where the program operated, and data from corresponding periods for a control region. The key finding is that there was no reduction in inappropriate IVIG use.

Why did the BC utilization control program fail to reduce inappropriate IVIG use? It involved the use and distribution of an IVIG Utilization Management Handbook to all BC physicians with guidelines for prescribers, and a more specific request form intended to reduce inappropriate use10. The fact that a guideline handbook does not in and of itself alter physician behavior is hardly surprising given the abundant literature showing that physician guidelines do not consistently alter behavior20,21. More surprising, though, is the apparent lack of effect of a special request form designed to reduce inappropriate orders for IVIG. A possible contributing factor to the lack of impact of the BC intervention was that the baseline utilization pattern in BC was already judged to be reasonably appropriate, but this alone does not fully explain the lack of effect. Perhaps the persistence of inappropriate use of IVIG after implementation of the special request form in BC suggests that the form is not *firmly* blocking orders for IVIG use in situations where use was inappropriate (for if it were, we would expect to see a precipitous drop in inappropriate IVIG use). Further, the form and related utilization control system may have permitted some questionable use to proceed, because it may not align fully with the indications that the RAND method identified to be inappropriate.

Utilization controls in other clinical areas have had some positive effects. For example, Samore et al22 used a utilization control program that reduced inappropriate utilization of antibiotics in community practice settings. And Bertakis et al23 successfully developed a utilization control program that targets patients through education to reduce inappropriate utilization of health services. More specifically, Constantine et al24 described a utilization control program in Atlantic Canada that may also have slightly reduced the frequency of inappropriate use of IVIG, though the evaluation of its effects is limited in its scope, and inappropriate use remained quite rampant despite its 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 transfusion25.

Effective reduction of inappropriate IVIG use will require 1) the development of more formal and vigorous utilization controls; and 2) targeted educational interventions; and, 3) formal evaluation of the control program after its implementation to ensure that it is having an effect on inappropriate use. The tools that we have developed for this study could be used for future evaluations of IVIG appropriateness in other jurisdictions.

Our study has limitations. Most notably, our evaluation of the utilization controls in BC is merely an observational pre-post study. The presence of a concurrent control province strengthens the evaluation, but this approach to evaluation still falls short of the inferences that could be drawn from a more definitive evaluation design such as a cluster randomized trial of utilization controls. A second limitation is that some years have passed since implementation of the utilization controls in BC. We intentionally focused our initial assessment of appropriateness around the years of the control program’s implementation, but there is now also a clear need for ongoing assessment of IVIG utilization appropriateness in more recent years. A third limitation is that our disappointing findings relating to the utilization control program in British Columbia do not shed light onto *why* the program had no effect. Physician interviews and/or surveys are one method that could be used to explore the underlying reasons.

IVIG is a therapy that is highly amenable to study of utilization using a tool like the RAND appropriateness method. The findings of our study highlight that use of this expensive and availability-limited therapy requires ongoing monitoring through repeated appropriateness evaluations, and that jurisdictions need to consider the implementation and evaluation of forceful utilization control programs.

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Table 1 Number of scenarios for assessing IVIG appropriateness, inappropriateness and uncertainty

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Appropriate | Inappropriate | Uncertain | Total number |
| Overall | 77 | 136 | 128 | 341 |
| By disease category |  |  |  |  |
| 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 |
| Others | 4 | 13 | 7 | 24 |

Table 2 Characteristics of new patients who received IVIG

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristics | Alberta Cases | | British Columbia Cases | | P-values |
|  | N | % of 958 | N | % of 1298 |  |
| Age |  |  |  |  |  |
| ≤ 6 years | 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 | <0.01 |
| Sex |  |  |  |  |  |
| Female | 439 | 45.8 | 615 | 47.4 |  |
| Male | 519 | 54.2 | 683 | 52.6 | 0.46 |
| Teaching Hospital |  |  |  |  |  |
| No | 127 | 13.3 | 645 | 49.7 |  |
| Yes | 831 | 86.7 | 653 | 50.3 | <0.01 |
| Diagnosis Category |  |  |  |  |  |
| Dermatology | 21 | 2.2 | 23 | 1.8 |  |
| Hematology | 288 | 30.1 | 441 | 34.0 |  |
| Immunology | 39 | 4.1 | 91 | 7.0 |  |
| Infectious Disease | 120 | 12.5 | 201 | 15.5 |  |
| Miscellaneous | 14 | 1.5 | 10 | 0.8 |  |
| Neurology | 165 | 17.2 | 233 | 18.0 |  |
| Obstetrics/Gynecology | 16 | 1.7 | 15 | 1.2 |  |
| Rheumatology | 123 | 12.8 | 189 | 14.6 |  |
| Transplant | 129 | 13.5 | 53 | 4.1 |  |
| Missing | 43 | 4.5 | 42 | 3.2 | <0.01 |
| Year |  |  |  |  |  |
| 2001 | 467 | 48.7 | 646 | 49.8 |  |
| 2003 | 491 | 51.3 | 652 | 50.2 | 0.63 |

Table 3 IVIG appropriateness for new patients by diagnosis category

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Diagnosis Category | Number of cases | Appropriate | | | Inappropriate | | | Uncertain | |
|  |  | n | % |  | n | % |  | N | % |
| Overall | 2256 | 1221 | 54.1 |  | 642 | 28.5 |  | 393 | 17.4 |
| Dermatology | 44 | 8 | 18.2 |  | 0 | 0.0 |  | 36 | 81.8 |
| Hematology | 729 | 397 | 54.5 |  | 294 | 40.3 |  | 38 | 5.2 |
| Immunology | 130 | 115 | 88.5 |  | 0 | 0.0 |  | 15 | 11.5 |
| Infectious Disease | 321 | 113 | 35.2 |  | 79 | 24.6 |  | 129 | 40.2 |
| Miscellaneous | 24 | 3 | 12.5 |  | 7 | 29.2 |  | 14 | 58.3 |
| Neurology | 398 | 304 | 76.4 |  | 29 | 7.3 |  | 65 | 16.3 |
| Obstetrics/ Gynecology | 31 | 10 | 32.3 |  | 12 | 38.7 |  | 9 | 29.0 |
| Rheumatology | 312 | 261 | 83.7 |  | 15 | 4.8 |  | 36 | 11.5 |
| Transplant | 182 | 10 | 5.5 |  | 147 | 80.8 |  | 25 | 13.7 |
| Missing | 85 | 0 | 0 |  | 59 | 69.4 |  | 26 | 30.6 |

Table 4 IVIG appropriateness for new patients by intervention group

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Year 2001 (prior to intervention) | | Year 2003 (post intervention) | | P-value for appropriateness (year 2001 versus 2003) | |
|  | N | % | n | % | Crude | Risk adjusted\* |
| Alberta Cases (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 |  |  |

Adjusted for age, sex, teaching hospital, and diagnosis category. (Risk adjusted and un-adjusted P-value <0.01 for appropriateness non-intervention group versus intervention group.