New Zealand Blood Service
The gift of life

Intragam® P audit within eight centres in New Zealand

Final Report

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February 2006

BACKGROUND

The place of Intravenous Immunoglobulin (IVIG) as replacement therapy in patients with primary and secondary immune deficiency is well established. IVIG is also widely employed as first line or adjuvant therapy, or as an alternative to plasmapheresis, in a variety of diseases attributed to an immune aetiology[1]. As a result it is currently the most widely used plasma product in the world[1]. The use of IVIG in immunomodulatory settings is supported by lower levels of evidence than its use in replacement therapy[2]. The relative ease of IVIG therapy is a factor in influencing its choice ahead of other established options.

The widespread off-label use of IVIG has become an urgent problem[2] in some countries. It has been stated that the same policy that is used for other high cost treatments should be used for IVIG as well, ie the application of such therapy should be based on proven efficacy such as controlled, double blind clinical trials. If such a criterion was applied then a significant percentage of off-label indications are found to lack an evidence base[2]. However it is recognised that for some particularly rare disorders, controlled clinical trials may not be feasible and examination of other lesser levels of evidence may be necessary.

In New Zealand, Intragam® P is licensed for use as replacement IgG therapy in primary immunodeficiency; myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; and congenital or acquired immune deficiency syndrome with recurrent infections. It is also licensed for immunomodulatory therapy in idiopathic thrombocytopenic purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count; allogeneic bone marrow transplantation and Kawasaki disease.[3]

Presently, there are no generally accepted guidelines for the use of IVIG in New Zealand. Data on appropriateness or otherwise of the use of IVIG is not available. The New Zealand Blood Service (NZBS) is guided by the Australian Health Minister's Advisory Council (AHMAC) indications for the conditional use of Intragam® P[4]. The AHMAC guidance aims to identify diseases for which IVIG might be an appropriate treatment. For some conditions it defines specific criteria to guide use in these conditions.

Responding to the increased demand for Intragam® P, the Auckland District Health Board (ADHB) established an IVIG committee. This group has developed recommendations for the appropriate use of IVIG. These go further than the AHMAC Guidelines in that they identify not only diseases where IVIG might be appropriate but also identify specific criteria for treatment with IVIG. This document is at its final draft stage. However, it does set down tighter and more specific guidelines.

AIM

The aim of this audit was to collect specific data on cases where Intragam® P has been used in major hospitals across New Zealand and to determine whether the usage conforms to the draft ADHB guidelines and the AHMAC guidelines[3].

The audit collected data prospectively from 13th September 2004 until 13th March 2005. An interim analysis of the audit was undertaken using the first two months' data and was reported previously.

METHOD

The audit included those patients who receive Intragam® P as an inpatient or outpatient. DHBs participating in the audit were Auckland, Waikato, Bay of Plenty, Mid Central, Capital & Coast, Canterbury, Otago and Southland. The participating DHBs were chosen based mainly whether the blood bank was managed by NZBS but also on use per capita.

Relevant clinical details of each patient were reviewed once only unless the clinical indication changed.

Data collection for each episode included patient demographics (Progesa number, NHI number, age, gender and weight), product data (the date of issue and the total course dose) and clinical data (the clinical diagnosis, the severity of the disease, blood tests where applicable and the AHMAC guidelines category).

The data was collated in a Microsoft Access database with restricted access, located on NZBS's internal network. No patient identifying data was included in the interim report or is included in this report.

On completion of the audit, the national blood management computer system, Progesa, was searched for the total dose received during the six months of the audit, the first ever date that the patient was recorded as having received Intragam® P and the first date the patient was tested for ABO blood group.

RESULTS

Demographics

466 episodes from 456 patients were captured during the audit. The median age was 43.6 years, median weight was 68kg and 54% were male. The eight DHBs contributed 22 –139 episodes each for the six month period (table 1).

Table 1. *Patient demographics and number of episodes by DHB.*

DHB	Median age *(years)*	Median weight *(kg)*	No of episodes
Auckland	29.9	60.0	139
Bay of Plenty	58.3	67.9	31
Canterbury	44.7	71.3	71
Capital & Coast	42.1	68.0	76
MidCentral	39.1	65.4	22
Otago	54.1	72.8	35
Southland	52.9	74.0	27
Waikato	55.1	70.5	65
Overall	43.6	68.0	466

AHMAC Catgerories

The majority (81%) of all episodes were in AHMAC category 1 (indications with convincing evidence of benefit) (table 2). 13% of episodes had a diagnosis not listed in the AHMAC guidelines or did not meet the criteria set down by the AHMAC guidelines.

Table 2. *Breakdown of episodes by AHMAC categories*

AHMAC category		Percentage *n=466*
Category 1	Indications with convincing evidence of benefit.	81%
Category 2	Indications with inconclusive evidence of benefit.	5%
Category 3	Conditions with convincing evidence that IVIG has no benefit.	1%
	No AHMAC category listed	13%

Of the 90 episodes not in Category 1 of the AHMAC guidelines (table 3), half were from diagnoses recognised by the draft ADHB guidelines. However the remaining half were an assortment of diagnoses, largely with a single patient per diagnosis.

Table 3. *Disorders with AHMAC category other than 1*

Disorder	n	AHMAC Category
Autoimmune haemolytic anaemia	4	2
Chronic Lymphocytic leukaemia, without hypogammaglobulinaemia and recurrent infections	3	Not listed
Immune thrombocytopenic purpura (ITP), as first line therapy, steroids not contraindicated	15	Not listed
Lymphoma	4	Not listed
Primary antibody deficiency (including CVID) with no record of IgG levels	9	Not listed
Prophylaxis or treatment of Chickenpox	4	Not listed
Prophylaxis or treatment of Tetanus	2	Not listed
Red cell aplasia, not due to Parvovirus B19	1	Not listed
Sepsis* - Neonate not part of INIS trial	6	2 / Not listed
Sepsis* - other than toxic shock or neonatal	2	Not listed
Sepsis* - Toxic shock syndrome	1	2
Solid organ transplantation	3	2
Other (see appendix 2)	14	2
Other (see appendix 2)	4	3
Other (see appendix 2)	18	Not listed

* AHMAC and ADHB differ in the way they approach sepsis.

Draft ADHB Guidelines

Although the draft ADHB guidelines have not been distributed outside ADHB until this audit, they appear to be covering the majority of patients at all DHBs with 72% of cases meeting the draft ADHB guidelines for Intragam® P use (table 4). Some variation is seen across the seven non-Auckland DHBs and this is probably explained only partly by clinical practice. Other factors in the variation include patient mix, especially for the DHBs with relatively small numbers.

Table 4. *Episodes meeting the draft ADHB guidelines by DHB*

DHB	n	Meets draft ADHB criteria	AHMAC Category 1
Auckland	139	88%	89%
Bay of Plenty	31	61%	84%
Canterbury	71	65%	75%
Capital & Coast	76	72%	83%
MidCentral	22	55%	82%
Otago	35	57%	71%
Southland	27	56%	70%
Waikato	65	68%	74%
Overall	466	72%	81%

The draft ADHB guidelines appear to be embracing the majority of clinical areas (table 5). It is interesting that Immunology only meets the ADHB guidelines in 82% of cases. Closer inspection of this reveals some Intragam® P issues for which antibody levels cannot be found. This is mainly due to the difficulty in tracking historic laboratory data. Another large group is antibody deficiency with recurrent chest infections but no mention of vaccination failure (as required by the guidelines). This may reflect difficulty in finding vaccination information, as these patients were all adults, or a clinical decision not to deliberately challenge the patient with a vaccination. This problem was peculiar to the antibody deficiency group of patients.

Table 5. *Categories meeting ADHB guidelines*

Category	n	Meets draft ADHB criteria	AHMAC Category 1
Haematology	112	74%	76%
Hyperimmune use	6	0%	0%
Immunology	140	82%	94%
Infections (Kawasaki's and sepsis)	30	73%	70%
Neurology	110	76%	100%
Transplantation	31	97%	90%
Other	37	0%	3%
Overall	466	72%	81%

Looking at the clinical categories across the eight DHBs (table 6), reveals some variation between DHBs. Close inspection of Haematology shows wide variation in the management of ITP with DHB's episodes meeting draft ADHB criteria ranging from 17-88%. However, some clinical settings which do not meet the ADHB criteria are treated with Intragam® P at some hospitals but not others. Chronic lymphocytic leukaemia, multiple myeloma, and lymphoma are notable examples of this. A few outliers are noted in Immunology but this is probably best explained but poor access to historic results. The variation in Infections is due to some DHBs using Intragam® P for sepsis (partly accepted by ADHB criteria) while others are only using it for Kawasaki's Disease (fully accepted). Neurology has a significant outlier in MidCentral DHB but this DHB is strongly affected by small case numbers (5 cases).

Table 6. *Percentage of episodes meeting ADHB criteria and total number in parentheses by category and DHB*

Category	Auckland	Bay of Plenty	Canterbury	Capital & Coast	MidCentral	Otago	Southland	Waikato
Haematology	93% (30)	70% (10)	50% (12)	82% (11)	40% (10)	80% (10)	38% (8)	86% (21)
Hyperimmune	0% (4)	0% (1)	-	-	-	-	-	0% (1)
Immunology	96% (54)	43% (14)	81% (21)	90% (20)	100% (5)	100% (5)	100% (2)	53% (19)
Infections (Kawasaki's and sepsis)	75% (12)	100% (3)	0% (1)	71% (7)	100% (2)	0% (2)	-	100% (3)
Neurology	89% (28)	100% (3)	76% (17)	70% (20)	20% (5)	55% (11)	75% (12)	93% (14)
Transplantation	90% (10)	-	100% (10)	100% (9)	-	100% (1)	100% (1)	-
Other	0% (1)	-	0% (10)	0% (9)	-	0% (6)	0% (4)	0% (7)

As the draft ADHB guidelines are more restrictive than the AHMAC guidelines, a number of episodes fell within Category 1 of the AHMAC guidelines but did not fall within the draft ADHB guidelines (table 7). All of these were for diagnoses covered by the draft ADHB guidelines but where the qualifying clinical condition of the patient was not met.

Table 7. *Episodes in AHMAC Category 1 not meeting ADHB Draft criteria*

Disorder	Limit	n
CLL	IgG < 6 but no recurrent infections or recurrent infection but IgG > 6	1
CIDP	Weakness not interfering with ADLs	3
CIDP	Weakness interfering with ADLs and on corticosteroids at initiation of Intragam® P, but too early to assess response to corticosteroids	4
CIDP	Weakness interfering with ADLs, steroids not tried	6
Guillain-Barre Syndrome	Able to walk > 10 paces independently, without respiratory compromise and has not had a plasma exchange	5
ITP	Pregnant, neonate of mother with ITP or steroids not used. No life-threatening haemorrhage	3
Multiple Myeloma	Recurrent infection but IgG > 6	1
Myasthenia Gravis	No severe bulbar or respiratory weakness and has NOT had a plasma exchange	4
IgM paraproteinaemic neuropathy	Not usually be considered a therapeutic option; would be considered on a case by case basis	1
Polymyositis	Not usually be considered a therapeutic option; would be considered on a case by case basis	4
Primary antibody deficiency	IgG > 3; no recurrent infections and vaccine unresponsiveness. May have subclass deficiency	17
Solid organ transplantation	Other than antibody mediated rejection	1

Dosing

The median dose was 0.9 g/kg. Doses showed a trimodal distribution (figure 1), with peaks around 0.6, 1 and 2 g/kg. Median doses for each disorder in the eight DHBs for which data had been captured were mostly similar (table 8). Some unusually high doses, up to 3.6g/kg, were seen.

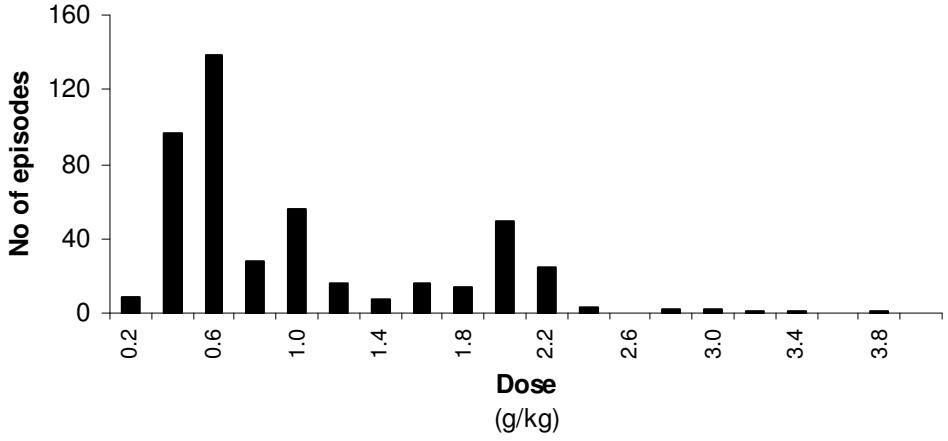


Figure 1. *Distribution of doses*

Table 8. Mean dose (g/kg) by disorder and centre

Disorder	Overall mean dose	Auckland	Bay of Plenty	Canterbury	Capital & Coast	MidCentral	Otago	Southland	Waikato
Acute leukaemia in childhood	0.5	0.5		0.5	0.5				
Allogeneic stem cell or bone marrow transplant	0.4	0.6		0.3	0.4		0.3	0.3	
Antenatal alloimmune thrombocytopenia	1.6	1.7					1.6		
Autoimmune haemolytic anaemia	1.8		1.6			2.0			1.9
Chronic Lymphocytic leukaemia	0.5	0.9	0.4	0.8	0.4	0.9	0.3	1.0	0.3
CIDP	1.1	1.1		1.4	0.9	1.5	0.6	1.2	1.5
Dermatomyositis	1.1	1.1							
Guillain-Barre Syndrome	1.5	1.6	2.5	1.9	0.4		1.5	1.8	2.0
HIV associated thrombocytopenia	2.0					2.0			
Immune thrombocytopenic purpura (ITP)	1.3	1.2	1.0	1.3	1.4	1.3	1.1	1.6	1.4
Kawasaki's	2.1	1.9	2.5		2.0	2.0			2.1
Lymphoma	0.5							0.5	0.5
Multifocal Motor Neuropathy	1.0	1.4		0.6	0.5				2.1
Multiple Myeloma	0.4		0.3	0.3	0.8	0.4		0.3	
Myasthenia Gravis	1.0					1.5	0.2	0.7	1.7
Polymyositis	1.4			2.0	0.4			1.7	
Primary antibody deficiency (including CVID)	0.5	0.5	0.4	0.5	0.4	0.6	0.4	0.4	0.5
Prophylaxis or treatment of Chickenpox	0.3	0.4							0.0
Prophylaxis or treatment of Tetanus	0.2	0.2	0.3						
Red cell aplasia	2.7	2.9							2.4
SCID, HyperIgM	0.6	0.8			0.4				
Sepsis - Neonate not part of INIS trial	0.9	1.3		1.0	0.7		0.5		
Sepsis - other than toxic shock or neonatal	0.9	0.8					1.0		
Sepsis - Toxic shock syndrome	1.8	1.8							
Solid organ transplantation	1.3	1.3							
Other	0.9	0.4		1.1	0.7		0.9	1.0	1.0

Using Progesa, the total dose issued to each patient in the audit was collated. As seen in a paper using retrospective NZHIS data, circulated in January this year as part of its NZBS' Demand Management initiative, relatively few diagnoses include most patients and consume the most Intragam® P (figure 2). Together, primary antibody deficiency, CIDP, ITP and Guillain-Barre accounted for 59% of all patients and 61% of all Intragam® P used over 6 months.

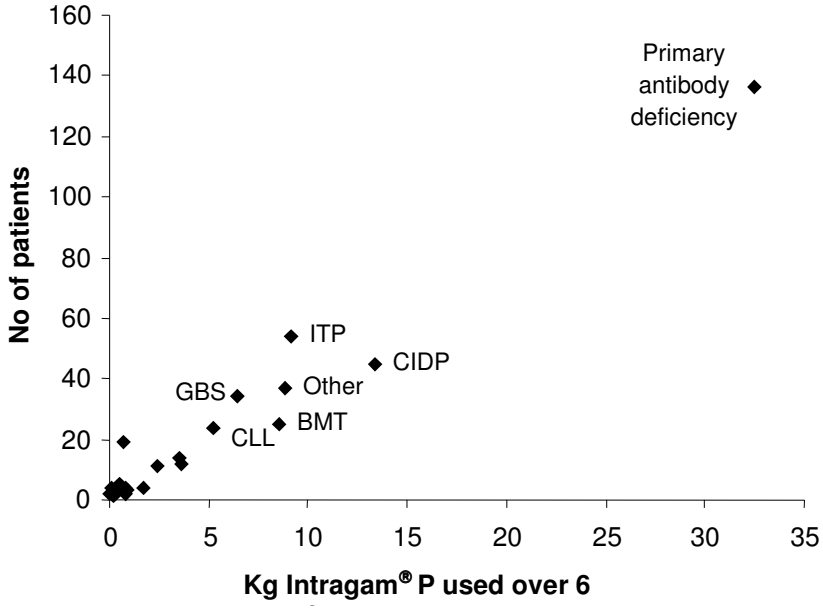
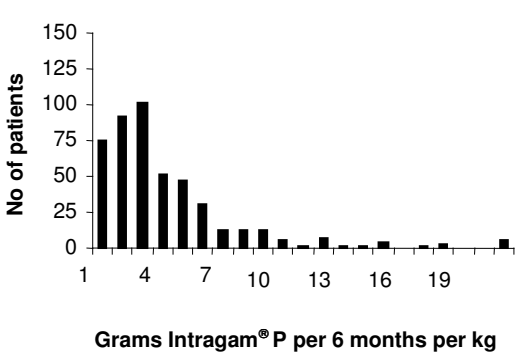


Figure 2. *Total Intragam® P issues by patient numbers*

High Volume Recipients

High volume recipients of Intragam® P were defined as having either a dose per kilogram per episode in the top 3% of the audit's doses nationally, or as having a a total dose over six months in the top 3% of the audit's total doses nationally. The cutoff of 3% was based on being more than two standard deviations above the mean (figure 3). The cutoffs were 800 g/6 months for total dose and 12g/kg/6months for total dose per kg bodyweight. Although the data is imperfect for this table, due to overlap of some high volume recipients across more than one DHB, it is apparent that, despite the small number of patients, high volume recipients contributed a significant proportion of DHB consumption (table 9).

Figures 3a and 3b: *Distribution of total dose over 6 months and total dose over 6months per kg*



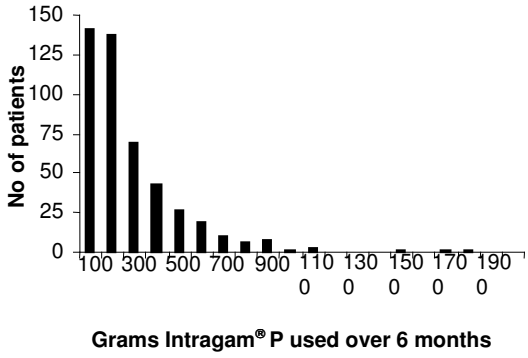


Table 9. *High volume recipients and their contribution to total DHB use*

DHB	n	High volume recipients *(g)*	DHB total use *(g)*	High volume recipients as % of total use
Auckland	7	4941	31263	16%
Bay of Plenty	0	0	5490	0%
Canterbury	1	819	13131	6%
Capital & Coast	8	7734	20997	37%
MidCentral	2	1608	6087	26%
Otago	0	0	7323	0%
Southland	3	3072	7440	41%
Waikato	2	1524	14151	11%
Overall	23	19698	105882	19%

High volume recipients were over-represented in certain diagnoses, notably allogeneic stem cell transplant recipients, primary antibody deficiency, acute leukaemia in childhood and chronic inflammatory demyelinating polyneuropathy (CIDP) (table 10).

Table 10. *High volume recipients and their representation within diagnoses*

Disorder	n	High volume recipients	Total Intragam® P used over 6 months on high volume recipients *(g)*	High volume use as a proportion of total use for diagnosis
Allogeneic stem cell or bone marrow transplant	27	6	5895	60%
Primary antibody deficiency (including CVID)	138	5	3978	12%
Acute leukaemia in childhood	13	4	2418	59%
CIDP	45	3	2613	20%
Red cell aplasia	2	1	810	98%
Immune thrombocytopenic purpura (ITP)	57	1	600	6%
Other: Bechet's Disease, Drug-induced toxic epidermal necrolysis, Rasmussen's Syndrome	37	3	3384	38%

Chronic and Repeated Recipients

Analysis of the first date that patients received Intragam® P shows that in 44% (192) of patients received Intragam® P for the first time during the audit (figure 4). 33% (145) received Intragam® P more than two years prior to being audited. An average of 4 patients commenced Intragam® P each month from 2 to 24 months prior to the audit.

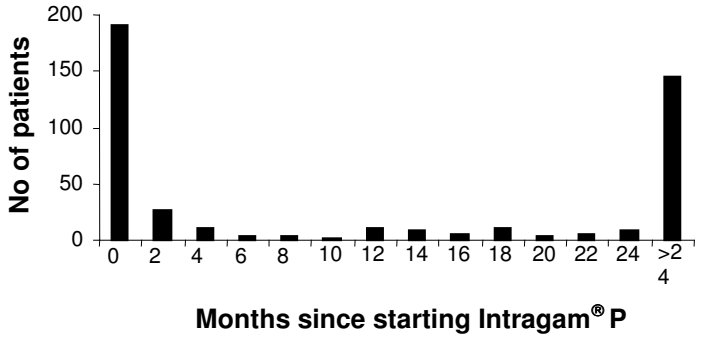


Figure 4. *Numbers of audit patients vs commencement on Intragam® P*

Paediatric Recipients

90 (20%) patients were less than 14 years old at entry into the audit. The median weight was 16.1 (0.7 – 56.3) kg and the median age was 4.3 (0.0 – 13.8) years. 23 (5% of all patients) had received Intragam® P for the first time prior to this audit. 18 (4% of all patients) had received Intragam® P more than 6 months more before the commencement of the audit.

ABO Grouping

A recommendation in the product datasheet is that any group A or AB patients receiving high dose therapy should then be monitored for falls in haemoglobin. 38% of the recipients of this audit did not have an ABO group in Progesa. The percentage of ungrouped recipients where the dose was greater than 0.4g/kg was 37%.

LIMITATIONS

There were six Transfusion Nurse Specialists and a Medical Officer collecting data. This permitted a national audit to be performed, but inherently introduced a potential for observer inconsistency. An attempt to reduce this from occurring was made with the format of the form used to collect data and regular telephone and face to face meetings to clarify problems raised during the audit period.

Access to old notes and laboratory results was often difficult, due in part to changing computer systems and paucity of note-taking. This meant assessment of some patients' diagnoses and condition at commencement of Intragam® P was not as robust as other cases. In particular, for a number of patients with antibody deficiencies, it was not possible to determine if the patients fulfilled the draft ADHB guidelines.

CONCLUSION

The sustained rise in Intragam® P use is of concern both to blood services and funders, locally and internationally.

This report has shown that although a significant amount of Intragam® P is used for off-label indications, 81% of issues of Intragam® P met the requirements of the AHMAC guidelines' category 1, though there is some variation across DHBs. As the AHMAC guidelines are comprehensive in the number of disorders covered, it is of some concern that nearly one in five episodes were either for a diagnosis not listed by the AHMAC guidelines or for an indication that the AHMAC guidelines did not consider was evidence based. However it does need to be remembered that the AHMAC guidelines are now five years old and that, at least for some disorders, knowledge has accrued in that interval.

72% of issues meet the more restrictive draft ADHB guidelines. These guidelines provide criteria for diagnoses "to ensure the appropriate use of a valuable and limited resource". This means an episode may meet the requirements for category 1 in the AHMAC guidelines but not meet the criteria for the draft ADHB guidelines. Using Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as an example, Intragam® P would be accepted under AHMAC guidelines provided there was objective improvement at 3 months. The draft ADHB guidelines require sufficient weakness to interfere with important activities and having either failed steroids or not been able to use steroids (intolerant or contra-indicated). The diagnoses of all episodes accepted as Category 1 by the AHMAC Guidelines were included in the draft ADHB guidelines but not all these episodes met the more restrictive requirements of the draft ADHB guidelines.

As seen in previous reports by NZBS, the majority of Intragam® P use is restricted to very few diagnoses. Together, primary antibody deficiency, CIDP, ITP and Guillain-Barre accounted for 59% of all patients and 61% of all Intragam® P used over 6 months.

Similarly, high volume recipients, defines as receiving the top 3% of doses (either dose per kg per episode or total dose over 6 months), contributed up to a third of some DHBs' total use of Intragam® P. This information can be used to guide strategies to monitor or contain the use of Intragam® P. Such strategies would ideally be collaborative across many or all DHBs as the cost for patients prescribed Intragam® P is often borne by more than one DHB.

This audit provides data comparing mean doses for a wide variety of disorders across eight centres. However it is acknowledged that in patients on regular treatment, the mean dose may be influenced by the interval between infusions. Although it is not within the scope of this report to analyse each disorder individually, the data is made available (appendix 3) for centres to compare their own practice with other centres. It should also be noted that no attempt has been made to assess clinical outcome.

Positive direct antiglobulin tests and red cell haemolysis have been reported following high dose infusion of intravenous immunoglobulin due to the presence of anti-A, anti-B, and occasionally anti-D or other erythrocyte antibodies in the product. Such red cell sensitisation may cause crossmatching difficulties and transient haemolytic anaemia[1].

CSL, the manufacturer of Intragam® P, therefore recommends that all patients receiving high dose IVIG (>0.4 g/kg every 4 weeks) should have a pre-infusion ABO blood group determined and have their haemoglobin monitored in the days following therapy for evidence of clinically significant haemolysis[3]. Only 38% of such patients in this audit had an ABO blood group in the Progesa system. It is possible that some of the patients had been grouped prior to Progesa and that other patients were monitored for haemolysis regardless of ABO group. However, it seems that there is a lack of awareness of this recommendation for a large proportion of patients.

A little over half of Intragam® P recipients identified in this audit had received Intragam® P prior to the audit as well, suggesting they had indications for chronic or repeated use. These patients accrued at a rate of 11% per year. While its not possible through this audit to identify the rate at which chronic recipients stopped receiving Intragam® P, the rate of accrual of chronic and repeated use patients may be helpful in understanding the steadily increasing use of Intragam® P. It is interesting to note that the accrual rate is not dissimilar to the national average increase of 8% pa over the last 8 years.

A smaller component of the rise in use is the chronic or repeated use of Intragam® P in growing children. Only 5% of recipients fell into this group, with their growth potentially accounting for less than half a percent overall increase in Intragam® P.

Dr R Charlewood
October 2005

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APPENDICES

Appendix 1: *Use of Intragam® P over 6 months by disorder and patient numbers*

Disorder	Intragam® P used (g)	Proportion of total use	No of patients
Primary antibody deficiency (including CVID)	32499	32%	136
CIDP	13356	13%	45
Immune thrombocytopenic purpura (ITP)	9198	9%	54
Other	8874	9%	37
Allogeneic stem cell or bone marrow transplant	8541	8%	25
Guillain-Barre Syndrome	6396	6%	34
Chronic Lymphocytic leukaemia	5262	5%	24
Acute leukaemia in childhood	3591	4%	12
Multifocal Motor Neuropathy	3474	3%	14
Myasthenia Gravis	2406	2%	11
Solid organ transplantation	1704	2%	4
Autoimmune haemolytic anaemia	858	1%	3
Polymyositis	846	1%	4
Red cell aplasia	828	1%	2
SCID, HyperIgM	822	1%	2
Kawasaki's	732	1%	19
Multiple Myeloma	465	0%	5
Lymphoma	420	0%	4
Antenatal alloimmune thrombocytopenia	318	0%	2
Sepsis - Toxic shock syndrome	252	0%	3
Dermatomyositis	240	0%	2
HIV associated thrombocytopenia	180	0%	1
Sepsis - other than toxic shock or neonatal	90	0%	2
Prophylaxis or treatment of Chickenpox	72	0%	4
Prophylaxis or treatment of Tetanus	48	0%	2
Sepsis - Neonate not part of INIS trial	24	0%	6
	101496	100%	457

Appendix 2: *Use of Intragam® P in disorders not mentioned in the ADHB guidelines*

Disorder	AHMAC Category	Number of episodes	Intragam® P used over 6 months (g)	Proportion of all Intragam® P use (%)
ANCA positive vasculitis/Wegeners	2	1	24	0.02%
Asthma, severe with recurrent infected sputum	2	1	429	0.42%
Bechet's Disease	Not listed	1	1680	1.66%
Diabetic amyotrophy & peripheral neuropathy. Giant cell arteritis.	2	1	90	0.09%
Diabetic neuropathy ?immunological overlap	2	1	81	0.08%
Diabetic segmental peripheral neuropathy	Not listed	1	90	0.09%
Drug induced Toxic epidermal necrolysis	Not listed	1	900	0.89%
Eaton Lambert Syndrome	Not listed	1	180	0.18%
Encephalitis, acute disseminating with bilateral optic neuritis.	Not listed	1	21	0.02%
Encephalitis, viral	2	1	102	0.10%
Encephalomyelitis, acute disseminating	Not listed	1	168	0.17%
Epilepsy (Rasmussen's Syndrome)	2	2	984	0.97%
Epilepsy with acquired aphasia (Landau Kleffer Syndrome)	Not listed	1	240	0.24%
Epilepsy, intractable	2	1	342	0.34%
Epilepsy, intractable secondary to linear sebaceous syndrome	2	1	81	0.08%
HDN	2	3	18	0.02%
Hyper IgE syndrome	Not listed	1	240	0.24%
Hyper IgE Syndrome with severe eczema	Not listed	1	96	0.09%
Multiple Sclerosis	3	1	126	0.12%
Multiple sclerosis & cerebellar ataxia	3	1	171	0.17%
Multiple sclerosis, atypical childhood with demyelinating encephalitis & seizures.	3	1	672	0.66%
Multiple Sclerosis; relapsing remitting	3	1	0	0.00%
Myopathy ? Inclusion body myositis	Not listed	1	63	0.06%
Myositis, sporadic inclusion body	Not listed	1	0	0.00%
Opsoclonus Myoclonus	2	1	216	0.21%
Peripheral neuropathy, anti-mag ?secondary to chemo	1	1	42	0.04%
Peripheral neuropathy, post viral sensory	Not listed	1	336	0.33%
Platelet antibodies	Not listed	1	528	0.52%
Post Polio Syndrome	Not listed	1	432	0.43%
Pyoderma Gangrenosum	Not listed	1	120	0.12%
Sacral plexopathy, non compressive lumbar of undetermined cause	Not listed	1	192	0.19%
Stevens-Johnson Syndrome	Not listed	1	42	0.04%
Stiff man syndrome	2	1	24	0.02%
Tolosa-Hunt syndrome	Not listed	1	144	0.14%
Total		37	8874	8.74%

Appendix 3: *Disorders, Intragam® P use, average dose and compliance with guidelines by DHB*

DHB	Disorder	n	Intragam® P use (g / 6 months)	% meet ADHB criteria	AHMAC cat 1 (%)	Dose (g/kg)
Auckland	Acute leukaemia in childhood	10	3093	100%	100%	0.5 (0.3 - 0.7)
Auckland	Allogeneic stem cell or bone marrow transplant	6	1347	100%	100%	0.6 (0.5 - 0.9)
Auckland	Antenatal alloimmune thrombocytopenia	1	312	100%	100%	1.7 (1.7 - 1.7)
Auckland	Chronic Lymphocytic leukaemia	1	0	100%	100%	0.9 (0.9 - 0.9)
Auckland	CIDP	10	2154	90%	100%	1.1 (0.4 - 2.0)
Auckland	Dermatomyositis	2	240	100%	100%	1.1 (1.0 - 1.1)
Auckland	Guillain-Barre Syndrome	14	2733	86%	100%	1.6 (0.3 - 2.3)
Auckland	Immune thrombocytopenic purpura (ITP)	17	2958	88%	88%	1.2 (0.4 - 2.1)
Auckland	Kawasaki's	6	168	100%	100%	1.9 (1.5 - 2.0)
Auckland	Multifocal Motor Neuropathy	2	324	100%	100%	1.4 (1.2 - 1.6)
Auckland	Other	1	24	0%	0%	0.4 (0.4 - 0.4)
Auckland	Primary antibody deficiency (including CVID)	53	14334	96%	98%	0.5 (0.1 - 1.5)
Auckland	Prophylaxis or treatment of Chickenpox	3	63	0%	0%	0.4 (0.2 - 0.5)
Auckland	Prophylaxis or treatment of Tetanus	1	0	0%	0%	0.2 (0.2 - 0.2)
Auckland	Red cell aplasia	1	810	100%	100%	2.9 (2.9 - 2.9)
Auckland	SCID, HyperIgM	1	720	100%	100%	0.8 (0.8 - 0.8)
Auckland	Sepsis - Neonate not part of INIS trial	2	9	0%	0%	1.3 (1.0 - 1.7)
Auckland	Sepsis - other than toxic shock or neonatal	1	18	0%	0%	0.8 (0.8 - 0.8)
Auckland	Sepsis - Toxic shock syndrome	3	252	100%	67%	1.8 (1.5 - 2.0)
Auckland	Solid organ transplantation	4	1704	75%	25%	1.3 (0.4 - 2.0)
Bay of Plenty	Autoimmune haemolytic anaemia	1	354	100%	0%	1.6 (1.6 - 1.6)
Bay of Plenty	Chronic Lymphocytic leukaemia	5	1854	100%	100%	0.4 (0.3 - 0.4)
Bay of Plenty	Guillain-Barre Syndrome	3	603	100%	100%	2.5 (2.0 - 3.4)
Bay of Plenty	Immune thrombocytopenic purpura (ITP)	3	138	33%	33%	1.0 (0.8 - 1.1)
Bay of Plenty	Kawasaki's	3	96	100%	100%	2.5 (1.8 - 3.6)
Bay of Plenty	Multiple Myeloma	1	42	0%	100%	0.3 (0.3 - 0.3)
Bay of Plenty	Primary antibody deficiency (including CVID)	14	2355	43%	93%	0.4 (0.3 - 1.0)
Bay of Plenty	Prophylaxis or treatment of Tetanus	1	48	0%	0%	0.3 (0.3 - 0.3)
Canterbury	Acute leukaemia in childhood	1	42	100%	100%	0.5 (0.5 - 0.5)
Canterbury	Allogeneic stem cell or bone marrow transplant	10	1560	100%	100%	0.3 (0.2 - 0.5)
Canterbury	Chronic Lymphocytic leukaemia	3	282	0%	33%	0.8 (0.4 - 1.0)
Canterbury	CIDP	9	3015	67%	100%	1.4 (0.3 - 2.0)
Canterbury	Guillain-Barre Syndrome	3	393	100%	100%	1.9 (1.8 - 1.9)
Canterbury	Immune thrombocytopenic purpura (ITP)	7	1332	57%	57%	1.3 (0.8 - 2.1)
Canterbury	Multifocal Motor Neuropathy	4	1122	100%	100%	0.6 (0.4 - 1.3)
Canterbury	Multiple Myeloma	1	27	100%	100%	0.3 (0.3 - 0.3)
Canterbury	Other	10	1362	0%	0%	1.1 (0.5 - 1.9)
Canterbury	Polymyositis	1	294	0%	100%	2.0 (2.0 - 2.0)
Canterbury	Primary antibody deficiency (including CVID)	21	3702	81%	90%	0.5 (0.3 - 0.5)
Canterbury	Sepsis - Neonate not part of INIS trial	1	0	0%	0%	1.0 (1.0 - 1.0)
Capital & Coast	Acute leukaemia in childhood	2	996	100%	100%	0.5 (0.5 - 0.6)
Capital & Coast	Allogeneic stem cell or bone marrow transplant	9	6363	100%	100%	0.4 (0.3 - 0.5)
Capital & Coast	Chronic Lymphocytic leukaemia	2	300	100%	100%	0.4 (0.4 - 0.4)
Capital & Coast	CIDP	8	3072	63%	100%	0.9 (0.4 - 2.0)
Capital & Coast	Guillain-Barre Syndrome	6	951	67%	100%	0.4 (0.3 - 0.4)
Capital & Coast	Immune thrombocytopenic purpura (ITP)	6	1518	67%	83%	1.4 (0.8 - 3.0)
Capital & Coast	Kawasaki's	5	177	100%	100%	2.0 (2.0 - 2.1)
Capital & Coast	Multifocal Motor Neuropathy	5	780	100%	100%	0.5 (0.4 - 0.7)
Capital & Coast	Multiple Myeloma	1	0	100%	100%	0.8 (0.8 - 0.8)
Capital & Coast	Other	9	2562	0%	0%	0.7 (0.4 - 2.0)
Capital & Coast	Polymyositis	1	120	0%	100%	0.4 (0.4 - 0.4)
Capital & Coast	Primary antibody deficiency (including CVID)	19	4047	89%	95%	0.4 (0.3 - 0.5)
Capital & Coast	SCID, HyperIgM	1	102	100%	100%	0.4 (0.4 - 0.4)

DHB	Disorder	n	Intragam® P use (g / 6 months)	% meet ADHB criteria	AHMAC cat 1 (%)	Dose (g/kg)
Capital & Coast	Sepsis - Neonate not part of INIS trial	2	9	0%	0%	0.7 (0.6 - 0.8)
MidCentral	Autoimmune haemolytic anaemia	1	144	0%	0%	2.0 (2.0 - 2.0)
MidCentral	Chronic Lymphocytic leukaemia	1	450	100%	100%	0.9 (0.9 - 0.9)
MidCentral	CIDP	3	738	33%	100%	1.5 (1.0 - 1.9)
MidCentral	HIV associated thrombocytopenia	1	180	100%	100%	2.0 (2.0 - 2.0)
MidCentral	Immune thrombocytopenic purpura (ITP)	6	1281	17%	50%	1.3 (0.8 - 3.0)
MidCentral	Kawasaki's	2	87	100%	100%	2.0 (2.0 - 2.0)
MidCentral	Multiple Myeloma	1	252	100%	100%	0.4 (0.4 - 0.4)
MidCentral	Myasthenia Gravis	2	435	0%	100%	1.5 (1.0 - 2.0)
MidCentral	Primary antibody deficiency (including CVID)	5	2520	100%	100%	0.6 (0.4 - 0.8)
Otago	Allogeneic stem cell or bone marrow transplant	1	504	100%	100%	0.3 (0.3 - 0.3)
Otago	Antenatal alloimmune thrombocytopenia	1	6	100%	100%	1.6 (1.6 - 1.6)
Otago	Chronic Lymphocytic leukaemia	2	216	100%	100%	0.3 (0.2 - 0.3)
Otago	CIDP	6	1902	50%	100%	0.6 (0.2 - 1.6)
Otago	Guillain-Barre Syndrome	2	240	100%	100%	1.5 (1.5 - 1.5)
Otago	Immune thrombocytopenic purpura (ITP)	7	1017	71%	71%	1.1 (0.4 - 2.0)
Otago	Myasthenia Gravis	3	1065	33%	100%	0.2 (0.2 - 0.3)
Otago	Other	6	1035	0%	0%	0.9 (0.2 - 1.6)
Otago	Primary antibody deficiency (including CVID)	5	1260	100%	100%	0.4 (0.3 - 0.8)
Otago	Sepsis - Neonate not part of INIS trial	1	6	0%	0%	0.5 (0.5 - 0.5)
Otago	Sepsis - other than toxic shock or neonatal	1	72	0%	0%	1.0 (1.0 - 1.0)
Southland	Allogeneic stem cell or bone marrow transplant	1	36	100%	100%	0.3 (0.3 - 0.3)
Southland	Chronic Lymphocytic leukaemia	1	288	0%	0%	1.0 (1.0 - 1.0)
Southland	CIDP	4	1512	100%	100%	1.2 (0.4 - 2.6)
Southland	Guillain-Barre Syndrome	3	645	67%	100%	1.8 (0.7 - 2.7)
Southland	Immune thrombocytopenic purpura (ITP)	3	738	67%	67%	1.6 (0.8 - 2.1)
Southland	Lymphoma	3	240	0%	0%	0.5 (0.3 - 0.5)
Southland	Multiple Myeloma	1	144	100%	100%	0.3 (0.3 - 0.3)
Southland	Myasthenia Gravis	3	264	100%	100%	0.7 (0.5 - 0.8)
Southland	Other	4	2325	0%	25%	1.0 (0.5 - 1.6)
Southland	Polymyositis	2	432	0%	100%	1.7 (1.7 - 1.8)
Southland	Primary antibody deficiency (including CVID)	2	816	100%	100%	0.4 (0.3 - 0.6)
Waikato	Autoimmune haemolytic anaemia	2	714	100%	0%	1.9 (1.6 - 2.1)
Waikato	Chronic Lymphocytic leukaemia	9	1872	100%	100%	0.3 (0.1 - 0.4)
Waikato	CIDP	5	963	80%	100%	1.5 (0.4 - 2.2)
Waikato	Guillain-Barre Syndrome	3	831	100%	100%	2.0 (1.9 - 2.2)
Waikato	Immune thrombocytopenic purpura (ITP)	8	1299	88%	88%	1.4 (0.4 - 2.1)
Waikato	Kawasaki's	3	204	100%	100%	2.1 (2.0 - 2.2)
Waikato	Lymphoma	1	180	0%	0%	0.5 (0.5 - 0.5)
Waikato	Multifocal Motor Neuropathy	3	1248	100%	100%	2.1 (1.9 - 2.4)
Waikato	Myasthenia Gravis	3	642	100%	100%	1.7 (0.8 - 2.1)
Waikato	Other	7	1566	0%	0%	1.0 (0.0 - 2.0)
Waikato	Primary antibody deficiency (including CVID)	19	4605	53%	79%	0.5 (0.2 - 1.0)
Waikato	Prophylaxis or treatment of Chickenpox	1	9	0%	0%	0.0 (0.0 - 0.0)
Waikato	Red cell aplasia	1	18	0%	0%	2.4 (2.4 - 2.4)

Appendix 4: *High volume recipients, defines as the top 3% of recipients by dose per kilogram over 6 months or total dose over 6 months, by DHB and disorder*

DHB	Disorder	6 month total dose *(g)*	6 month total dose per kilogram *(g/kg)*	Weight *(kg)*
Auckland	Acute leukaemia in childhood	540	13.8	39
Auckland	Acute leukaemia in childhood	882	17.3	51
Auckland	Allogeneic stem cell or bone marrow transplant	126	18.0	7
Auckland	Allogeneic stem cell or bone marrow transplant	765	16.3	47
Auckland	Primary antibody deficiency (including CVID)	810	8.4	97
Auckland	Primary antibody deficiency (including CVID)	1008	20.6	49
Auckland	Red cell aplasia	810	14.7	55
Canterbury	CIDP	819	8.3	99
Capital & Coast	Acute leukaemia in childhood	456	12.5	36.5
Capital & Coast	Acute leukaemia in childhood	540	14.3	37.7
Capital & Coast	Allogeneic stem cell or bone marrow transplant	765	17.2	44.5
Capital & Coast	Allogeneic stem cell or bone marrow transplant	1080	14.4	75
Capital & Coast	Allogeneic stem cell or bone marrow transplant	1404	16.3	86
Capital & Coast	Allogeneic stem cell or bone marrow transplant	1755	26.9	65.2
Capital & Coast	CIDP	930	11.1	84
Capital & Coast	Other	804	8.9	90
MidCentral	Immune thrombocytopenic purpura (ITP)	600	45.8	13.1
MidCentral	Primary antibody deficiency (including CVID)	1008	20.2	50
Southland	CIDP	864	10.5	82
Southland	Other	1680	22.7	74
Southland	Primary antibody deficiency (including CVID)	528	13.4	39.5
Waikato	Other	900	9.5	95
Waikato	Primary antibody deficiency (including CVID)	624	14.2	44