# Intragam P audit within ten centres in New Zealand

## Final Report


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October 2015

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## EXECUTIVE SUMMARY

In New Zealand the use of immunoglobulin has increased from 141,552 grams in financial year (FY) 2001/02 to 333,893 grams in FY 2014/15, an increase of 136% averaging 10.4% per annum over the period. The rate of growth has increased significantly during the last 2 years and is currently running at approximately 13% per annum. The growing demand for immunoglobulin now drives plasma procurement both in New Zealand and in most developed countries. NZBS is struggling to increase plasma collection to meet the increasing clinical use of the product and has recently announced an intention to import a commercial immunoglobulin in order to ensure certainty of supply. The financial impact of the increase in clinical use of immunoglobulin products is also raising concerns in many DHBs. Use of immunoglobulin in New Zealand however remains modest in international terms and is currently running at 73g/1000 population. The rate of increase in Australia has been running at around 11% per annum for several years and by July 2014 was 172g/1000 population.

Intragam P, an intravenous immunoglobulin product produced by CSL Behring Australia from plasma collected in New Zealand, remains the principal immunoglobulin product in New Zealand and accounts for 90% of total use of the products. A subcutaneous product (Evogam) was introduced in 2012 and is primarily used in patients with primary immunodeficiency. Currently it accounts for just under 10% of total immunoglobulin use.

Immunoglobulin is an expensive product (currently $88.50/gram). The total cost to the New Zealand public health sector in FY 2014/15 was over $29 million. This high cost combined with the current rate of increase in use necessitates a review of how the products are accessed. Similar concerns have been identified in Australia and England. Both countries have developed evidence based guidelines for use of immunoglobulin products and have used these to implement governance systems. These aim to improve appropriateness of use and in doing so improve transparency to support future planning. Both sets of guidelines have been published. The Department of Health in England published the second edition of the 'Clinical guidelines for immunoglobulin use' in 2011[4]. The Australian National Blood Authority (NBA) published the second edition of the 'Criteria for the clinical use of intravenous immunoglobulin in Australia' in 2012'[5].

The current audit aimed to evaluate the use of Intragam P in New Zealand against the criteria documented in the NBA (2012) and Department of Health (2011) guidelines. The secondary aims of this audit were: to compare the findings to those of a similar audit undertaken by NZBS in 2005; to identify any changes and/or improvements in practice; and to review any variance in clinical use across the regions.

Recipients of Intragam P during FY 2012/13 at the participating DHBs were identified from the NZBS blood management system, eProgesa. Data for this retrospective audit of patients attending the DHBs' main hospitals was obtained from the ten participating District Health Boards (Auckland, Canterbury, Capital & Coast, Counties Manukau, Hawkes Bay, MidCentral, Northland, Southern, Tairawhiti and Waikato). These ten DHBs currently account for 72% of all Intragam P issued in New Zealand.

The audit comprised a retrospective review of 891 episodes (a prescription for a new clinical indication) involving 864 patients covering the use of 207,792 grams of Intragam P during FY 2012/13. Records of eight patients could not be located and hence 883 patient episodes were evaluated. In the 2005 audit 90% of Intragam P was used for treatment of five disorders (primary immunodeficiency, secondary immunodeficiency, Guillain-Barré syndrome, Chronic Inflammatory Demyelinating Polyneuropathy, and Immune Thrombocytopenic Purpura). Information on treatment episodes for these disorders was documented in greater detail in the audit tool than was the case with the other diagnoses. All treatment episodes were however assessed against both the qualification and review criteria included in the guidelines. Interestingly the proportion of Intragam P used for these five diseases has fallen to 75% of total use. The remaining 25% of Intragam P is now being used in over 100 specific conditions.

Compliance with guidelines varies from indication to indication, as might be expected. Both sets of guidelines set qualification criteria for each clinical indication and also identify specific review requirements to determine the appropriateness of on-going use. When assessed against the NBA guidelines, overall 73% of patient episodes (88% by grams) met the qualification criteria and 76% the review criteria (86% by grams). Correspondingly, 64% of patient episodes (73% by grams) met the NHS qualifying criteria and 82% met the review criteria (88% by grams).

The compliance levels for the 'Big 5' and 'other' indications are shown in the table below. A small number of diagnoses treated within the audit could not be specifically found in the guidelines. These indications were classified as non-compliant.

| **Diagnosis** | **% total grams use** | **Number of Patient episodes and % of all episodes** | **NBA guideline** | | **NHS guideline** | |
|---|---|---|---|---|---|---|
| | | | **Number and % Patients complying with Qualification Criteria** | **Number and % Patients complying with Review Criteria** | **Number and % Patients complying with Qualification Criteria** | **Number and % Patients complying with Review Criteria** |
| Primary Immunodeficiency | 30% | 172 (19.5%) | 152 (88%) | No criteria | 152 (88%) | No criteria |
| Secondary Immunodeficiency | 18% | 186 (21%) | 83 (45%) | 136 (73%) | 9 (5%) | 165 (89%) |
| CIDP | 16% | 65 (7.4%) | 47 (72%) | 49 (75%) | 25 (38%) | 50 (77%) |
| ITP | 6% | 98 (11.1%) | 92 (94%) | 98 (100%) | 90 (92%) | 95 (97%) |
| Guillain-Barré Syndrome | 6% | 65 (7.4%) | 48 (74%) | 58 (89%) | 49 (75%) | 52 (80%) |
| Other conditions | 24% | 297 (33.6%) | 219 (74%) | 200 (67%) | 242 (81%) | 221 (74%) |
| Total evaluable patients episodes | 100% | 883 (100%) | 641 (73%) | 541* (76%) | 567 (64%) | 583* (82%) |

* excludes PID patients

Data capture for the audit was undertaken by seven Transfusion Nurse Specialists. This inherently introduced a potential for observer inconsistency, both in interpreting the guidelines as well as patients' notes. Considerable efforts were devoted to reducing this. Nonetheless it may have impacted on the overall results of the audit. It is important to bear in mind that since the audit was not conducted by specialists in the areas of the patients' illnesses, it is possible that some clinical nuances may have been lost by the auditors. Access to old notes and laboratory results was often difficult, due in part to a 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. It is also important to remember that for long term recipients of Intragam P treatment will have commenced prior to the criteria being developed. Furthermore many clinicians will not have been aware of the guidelines used in the audit and will therefore not have documented many aspects of the qualification and review criteria. For this reason caution should be made in assuming that identified non-compliance with the criteria corresponds to inappropriate use of the product. Nonetheless the data suggests that there is room for improvement and that potentially a more formal approach to approval for the products might assist in reducing the current rate of increase in use.

NZBS utilises a pre-approval process for accessing Intragam P. This is however used inconsistently by different DHBs. Requests for the product are assessed against the guidelines but the strict qualification criteria are not currently enforced. A number of DHBs have indicated a desire to move to a more formal process for accessing these products. Tools for simplifying peer or expert review at the initiation and review of Intragam P treatment can be expected to improve compliance. This would assist the smaller DHBs, whose use appears to be climbing at a faster rate than the larger DHBs, as well as larger DHBs who see a substantial financial outlay in Intragam P. Introduction of this type of process will require agreement with participating DHBs. This would require identification of a specific set of qualification and review criteria and a process for review of requests falling outside of the criteria. The Australian guidelines will likely be most appropriate given the close clinical contacts between New Zealand and Australia. NZBS is currently developing an electronic approval process which will provide better information and enable easier reporting to DHBs and this could form the first step in the development of a broader governance process.

## INTRODUCTION

Intravenous immunoglobulin (IVIg) was first used in 1952 to treat immunodeficiency, but only as an immunomodulatory agent, for ITP, from 1982. Its use has expanded to a large number of conditions and with that, increasing the cost to DHBs. In New Zealand the use of immunoglobulin has increased from 141,552 grams in the 2001/02 financial year (FY) to 333,893 grams in FY 2014/15. The overall increase in use over the period is 136% or an average annual growth of 10.4%. The rate of growth has increased significantly during the last 2 years and is currently running at approximately 13% per annum. The growing demand for immunoglobulin now drives plasma procurement both in New Zealand and in most developed countries. NZBS is struggling to increase plasma collection to meet the increasing clinical use of the product and has recently announced an intention to import a commercial immunoglobulin in order to ensure certainty of supply. The financial impact of the increase in clinical use of immunoglobulin products is also raising concerns in many DHBs. Use of immunoglobulin in New Zealand however remains modest in international terms and is currently running at 73g/1000 population. The rate of increase in Australia has been running at around 11% per annum for several years and by July 2014 was 172g/1000 population.

Intragam P, an intravenous immunoglobulin product produced by CSL Behring Australia from plasma collected in New Zealand, remains the principal immunoglobulin product in New Zealand and accounts for 90% of total use of the products. A subcutaneous product (Evogam) was introduced in 2012 and is primarily used in patients with primary immunodeficiency. Currently it accounts for just under 10% of total immunoglobulin use in New Zealand.

An audit conducted in 2005 by NZBS[1] concluded that, despite the wide variety of possible indications, a small set of disorders accounted for most IVIg use. This was in keeping with a Canadian study[2] where most use was for licensed or appropriate indications. The majority of off-label use was supported by medical literature. In Massachusetts, Darabi[3] also found that a few indications accounted for most of their use. Unfortunately, in many areas the evidence available is not robust due to the rarity of the conditions treated. As a result, IVIg is sometimes considered only as second or third line therapy when standard management has proven to be ineffective, poorly tolerated or contraindicated.

Immunoglobulin is an expensive product (currently $88.50/gram). The total cost to the New Zealand public health sector in FY 2014/15 was over $29 million. This high cost combined with the current rate of increase in use necessitates a review of how the products are accessed. Similar concerns have been identified in Australia and England. Both countries have developed evidence based guidelines for use of immunoglobulin products and have used these to implement governance systems. These aim to improve appropriateness of use and in doing so improve transparency to support future planning. Both sets of guidelines have been published. The Department of Health in England published the second edition of the 'Clinical guidelines for immunoglobulin use' in 2011[4]. The Australian National Blood Authority (NBA) published the second edition of the 'Criteria for the clinical use of intravenous immunoglobulin in Australia in 2012'[5].

Other guidelines have also been developed. These include 'The use of IVIg in neurological disease' which was updated in 2008 during the IVIg in Neurological Disease Asia Pacific Symposium (INDAPS)[6] and the 'Consensus recommendations for the use of immunoglobulin replacement therapy in immune deficiency' in 2009 by Asia Pacific Immunoglobulin in Immunology Expert Group (APIIEG)[7]. No single guideline has been adopted in New Zealand. The draft Auckland DHB guideline, used in NZBS's previous audit in 2005, remains in draft.

NZBS utilises a pre-approval process for accessing Intragam P. This is however used inconsistently by different DHBs. Requests for the product are assessed against the guidelines but the strict qualification criteria are not currently enforced. A number of DHBs have indicated a desire to move to a more formal process for accessing these products. Tools for simplifying peer or expert review at the initiation and review of Intragam P treatment can be expected to improve compliance. This would also assist the smaller DHBs whose use appears to be climbing at a faster rate than the larger DHBs, as well as larger DHBs who see a substantial financial outlay in Intragam P. Introduction of this type

of process will require agreement with participating DHBs. This would require identification of a specific set of qualification and review criteria and a process for review of requests falling outside of the criteria. The Australian guidelines will likely be most appropriate given the close clinical contacts between New Zealand and Australia. NZBS is currently developing an electronic approval process which will provide better information and enable easier reporting to DHBs and this could form the first step in the development of a broader governance process.

## AIM OF THE AUDIT

The primary aim of this audit was to identify if the use of IVIg (Intragam P) in New Zealand meets the criteria documented in the NBA (2012) and NHS Department of Health (2011) guidelines.

The secondary aims of this audit were: to compare the findings to those of the 2005 NZBS audit; to identify any changes and/or improvements in practice; to review any variance in clinical use across the regions; and to identify if any under or over prescribing may exist.

## METHOD

Recipients of Intragam P at the participating DHBs were identified from the NZBS blood management system, eProgesa. The total dose of Intragam P issued to each recipient over the 12 months was identified. Data for this retrospective audit was obtained from the ten participating District Health Boards (Auckland, Canterbury, Capital & Coast, Counties Manukau, Hawkes Bay, MidCentral, Northland, Southern, Tairawhiti and Waikato). These ten DHBs currently account for 72% of all Intragam P issued in New Zealand

The clinical qualification and review criteria of recipients in the participating audit sites were audited for compliance to the NBA and NHS guidelines. Both inpatient and outpatient areas were included. The audit was retrospective in nature.

Data was collected using the NZBS blood management system eProgesa and the local DHB clinical records. Data collection included:

- Demographic data: age of patient at first issue in the audit, gender, weight (current)
- Hospital and DHB
- Clinical Indication: diagnosis and rationale
- Intragam P Dose: date of issue, gram/kilogram and frequency
- Qualifying criteria: met or not met
- Review Criteria: completed, not completed or yet to be achieved
- For the five commonest conditions (from the previous audit), the specific qualifying and review criteria that had been met or not met.

Relevant clinical details of every patient were reviewed once only unless the clinical indication, even for the same condition, changed. For example, a patient with idiopathic thrombocytopenia purpura (ITP) may receive Intragam P for a life threatening haemorrhage on one occasion and in preparation for surgery on another so would be entered into the audit twice. The initial reason for commencing Intragam P was recorded for those patients who had received long-term repeat infusions of Intragam P. This mainly applied to those patients with Primary Immunodeficiency conditions but the principle was applied to other diseases.

The data was collated in a web-interfaced PostgreSQL database[8] with restricted access, located on a secure NZBS webserver. Only the Transfusion Nurse Specialist (TNS) collecting the data had access to any patient identifiers. All identifying data, including the NHI number, was removed prior to entering into the database.

The Health and Disability Ethics Committees Administrator confirmed that this audit did not require ethics review. Approval for participation in the audit was gained from the Hospital Transfusion Committees of the DHBs participating prior to commencement.

## RESULTS

### Demographics

*Use of Intragam P*

77% of all Intragam P issued within New Zealand during the 2012/13 financial year was audited (table 1). This involved auditing 891 episodes (a prescription for a new indication) from 864 patients covering the use of 207,792 grams of Intragam P, worth over $19 million at the time. Clinical records could not be located for eight recipients and so only 883 patient episodes were evaluated as part of the audit. 79% of Intragam P used during the year was used at DHBs included in the audit.

Apart from the six NZBS sites and one DHB site where a transfusion nurse specialist (TNS) is appointed, three other DHBs (Hawke's Bay, Northland and Tairawhiti) were audited by an NZBS TNS. Regrettably, due to a gap between resignation and appointment of their new transfusion nurse specialist, Waitemata DHB's recipients could not be audited.

**Table 1:** *Intragam P usage by DHB and whether the DHB was audited*

| DHB | Intragam P use pa (g) | Audit episodes | Population* | Intragam P (g) pa per 1000 population | Average age (years) | Average weight (kg) | Status |
|---|---|---|---|---|---|---|---|
| Auckland | 56,010 | 257 | 404,619 | 138 | 29 | 52 | audited |
| Canterbury | 31,995 | 141 | 466,407 | 69 | 39 | 59 | audited |
| Capital and Coast | 30,522 | 119 | 266,658 | 114 | 43 | 68 | audited |
| Counties Manukau | 12,351 | 75 | 433,086 | 29 | 44 | 62 | audited |
| Hawkes Bay | 7,260 | 27 | 148,248 | 49 | 40 | 66 | audited |
| MidCentral | 9,630 | 41 | 158,841 | 61 | 45 | 70 | audited |
| Northland | 8,349 | 35 | 148,440 | 56 | 36 | 61 | audited |
| Southern | 21,063 | 80 | 286,224 | 74 | 53 | 67 | audited |
| Tairawhiti | 2,250 | 7 | 44,463 | 51 | 40 | 54 | audited |
| Waikato | 28,362 | 109 | 339,192 | 84 | 50 | 71 | audited |
| Bay of Plenty | 17,343 | 73 | 194,931 | 89 | | | not audited |
| Hutt Valley | 5,571 | 21 | 136,101 | 41 | | | not audited |
| Lakes | 7,251 | 30 | 98,319 | 74 | | | not audited |
| Nelson Marlborough | 5,787 | 26 | 130,062 | 44 | | | not audited |
| South Canterbury | 666 | 5 | 53,877 | 12 | | | not audited |
| Taranaki | 5,043 | 22 | 104,277 | 48 | | | not audited |
| Wairarapa | 2,889 | 8 | 38,613 | 75 | | | not audited |
| Waitemata | 8,655 | 73 | 481,611 | 18 | | | not audited |
| West Coast | 855 | 4 | 31,326 | 27 | | | not audited |
| Whanganui | 2,583 | 9 | 62,211 | 42 | | | not audited |
| In audit | 207,792 | 891 | | | | | |
| Audited % | 79% | 77% | | | | | |
| Not audited | 56,643 | 271 | | | | | |

* 2012 population data from Dept of Statistics website

The use per 1000 population was based on usage within a DHB against the population living within the DHB. No accounting for inter district flow was made.

The increase in use of Intragam P in the audited DHBs has been significant over the last decade and continues to rise in the two years following the period covered by the audit (table 2). The data indicates that the increase is occurring not only in the larger DHBs but across the entire sector.

**Table 2:** *Immunoglobulin use in grams, including Evogam, in financial years 2004/2005 vs 2012/2013 and 2014/2015 with percentage rise compared with baseline audit in DHBs audited in this report compared with those not audited*

| | FY 04/05 | FY 12/13 | FY 14/15 |
|---|---|---|---|
| Total | 184,986 | 276,532 (149%) | 333,725 (180%) |
| Audited sites | 153,990 | 222,414 (144%) | 276,449 (180%) |
| Not audited | 30,996 | 54,119 (175%) | 57,276 (185%) |

Data per DHB is available in the respective DHB's demand management reports.

*Age and gender profile of recipients*

54% of patients were female. Age distribution was different to the usual distribution of blood components and products with a relatively flat age distribution and a small peak between the ages of 51 and 69 years (figure 1).

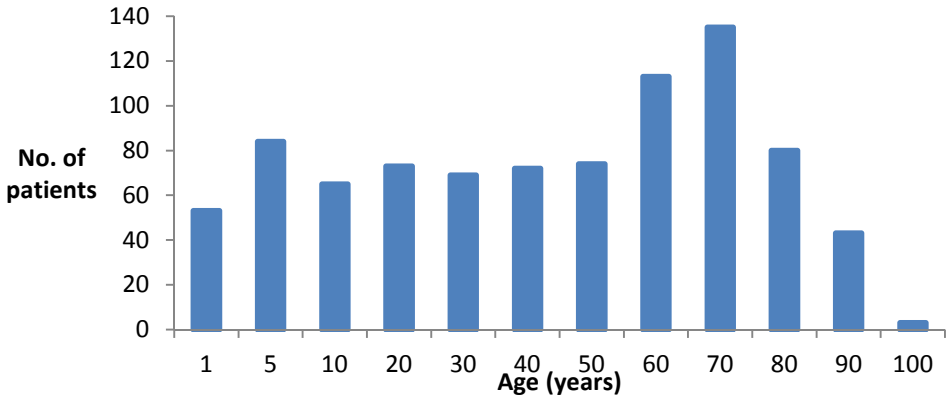


**Figure 1:** *age distribution of audited Intragam P recipients*

*Weight of recipients*

The dose of immunoglobulin is normally based on the weight of the patient (grams per kg). Both the Australian and NHS guidelines discuss the use of 'lean body weight' for this purpose. The Australian Guidelines identify that '*while there is some evidence for the use of dosing based on lean body weight, further research is required.*' The NHS guidelines identify that '*there is considerable interest in the use of ideal body weight-adjusted dosing of immunoglobulin, based on the view that drugs with a narrow therapeutic index are usually dose-adjusted by surface area or another formula to allow for the poorly perfused excess adipose tissue. The concept of using biological agents at their lowest effective dose is logical and may also contribute to minimisation of side-effects, some of which may be dose related. This would also save significant quantities of immunoglobulin.*' They go on to state '*there is a very limited evidence base, which is too weak to allow a firm recommendation, but there are some reports supporting this approach.'* Some sites in New Zealand are already using this approach. Specific data on this issue was not however collected during the audit.

A weight could be found for 95% of recipients. Weight distribution for recipients was similarly relatively flat with a peak in the 61-80 kg group (figure 2). 25% of patients weighed more than 80kg with only 7% of patients weighing more than 100kg.

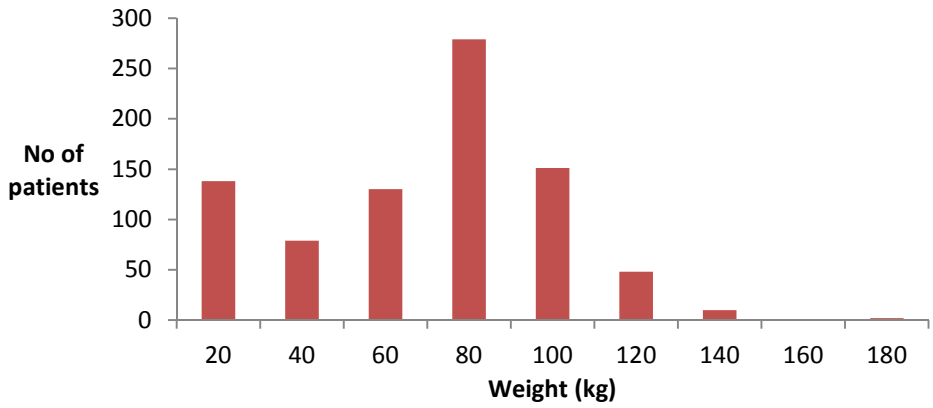


**Figure 2:** *weight distribution of audited Intragam P recipients (where weight available)*

## Disease-specific data

Compared with the 2005 audit, Intragam P use at the audited sites has risen by 137%. The 2005 audit was over six months, not a full year, so did not account for any seasonal variation that might exist in clinical use of the product. The increase in use is not even across the main disease categories. This data is shown in table 3. Of the 'Big 5' indications, only CIDP has shown a significant increase in percentage use. The data for PID underestimates use in this condition since a number of patients had transitioned to subcutaneous treatment between the 2 audits. When the data is adjusted to take this into account the change is 101%. However the data might be influenced by changing patterns of treatment whereby increasingly patients are diagnosed in the tertiary centres and subsequently receive immunoglobulin infusions at their base DHB. This would particularly affect chronic conditions such as PID, CIDP and secondary immunodeficiency. The key finding of the audit however is the very significant use outside of the five main indications which has increased to 288% over the period. In the current audit 24% of Intragam P use was in these other conditions compared to 10% in the 2005 audit.

**Table 3:** *Annualised usage of Intragam P by disease category from '04/05 vs '12/13 audits*

| Disorder | FY 04/05 (g pa) | FY 12/13 (g pa) | % change |
|---|---|---|---|
| Other | 17,748 | 51,072 | 288% |
| Chronic Inflammatory Demyelinating Polyneuropathy | 26,712 | 33,402 | 125% |
| Secondary hypogammaglobulinaemia | 36,558 | 37,086 | 101% |
| Guillain-Barré Syndrome | 12,792 | 12,375 | 97% |
| Primary Immunodeficiency | 64,998 | 61,722 | 95% |
| Idiopathic Thrombocytopenic Purpura | 18,396 | 12,135 | 66% |
| Overall | 177,204 | 207,792 | 117% |

## Limitations

The retrospective nature of this audit is associated with a number of limitations.

1. Data capture for the audit was undertaken by seven Transfusion Nurse Specialists. This inherently introduced a potential for observer inconsistency, both in interpreting the guidelines as well as patients' notes. Considerable efforts were devoted to reducing this. Nonetheless it may have impacted on the overall results of the audit.

2. The audit was not conducted by specialists in the areas of the patients' illnesses. It is therefore possible that some clinical nuances may have been lost by the auditors. Access to old notes and laboratory results was often difficult, due in part to a 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.

3. For many long term recipients of Intragam P treatment will have commenced prior to the criteria being developed. Furthermore many clinicians will not have been aware of the guidelines used in the audit and will therefore not have documented many aspects of the qualification and review criteria.

These limitations need to be considered when reviewing the results of the audit. Caution should be made in assuming that identified non-compliance with the criteria corresponds to inappropriate use of the product.

## Primary Immunodeficiency

### *Qualification and review criteria*

| Guideline | Australia | NHS |
|---|---|---|
| **Qualification criteria** | A specific PID diagnosis must be established under the supervision of a specialist clinical immunologist and the diagnosis | A specific PID diagnosis must be established by a clinical immunologist |
| **Exclusion criteria** | The following conditions should not be approved under this indication:<br>1. Miscellaneous hypogammaglobulinaemia<br>2. Specific antibody deficiency<br>3. IgG subclass deficiency | |
| **Review criteria** | Review criteria for primary immunodeficiency diseases with antibody deficiency are not mandated | Outcome measures are not required |

Primary immunodeficiency (PID) accounted for 172 of the 864 (19.9%) episodes in the audit and for 30% of total grams of Intragam P used during the period. This underestimates the amount of immunoglobulin used in PID since a number of patients were receiving subcutaneous replacement treatment at the time. If this is included then total use of immunoglobulin for PID at these DHBs increases to 38% of total use in 2012/13. Average use of Intragam P per patient was 359g/year. Only ten patients were aged under 16 years of age. This may reflect the high level of subcutaneous immunoglobulin used in paediatric primary immunodeficiency.

**Table 4:** *Primary immunodeficiency: compliance with NBA and NHS qualification criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 23,952 (100%) | 70 (100%) | 23,940 (100%) | 69 (99%) | 23,952 | 70 |
| Canterbury | 8,043 (100%) | 22 (100%) | 8,043 (100%) | 22 (100%) | 8,043 | 22 |
| Capital and Coast | 9,012 (91%) | 22 (92%) | 9,588 (96%) | 23 (96%) | 9,948 | 24 |
| Counties Manukau | 876 (81%) | 6 (86%) | 1,086 (100%) | 7 (100%) | 1,086 | 7 |
| Hawkes Bay | 972 (82%) | 2 (67%) | 1,188 (100%) | 3 (100%) | 1,188 | 3 |
| MidCentral | 1,650 (100%) | 4 (100%) | 1,650 (100%) | 4 (100%) | 1,650 | 4 |
| Northland | 4,386 (90%) | 12 (92%) | 4,386 (90%) | 12 (92%) | 4,854 | 13 |
| Southern | 1,563 (30%) | 5 (36%) | 1,563 (30%) | 5 (36%) | 5,211 | 14 |
| Waikato | 3,627 (63%) | 9 (60%) | 2,856 (49%) | 7 (47%) | 5,790 | 15 |
| Overall | 54,081 (88%) | 152 (88%) | 54,300 (88%) | 152 (88%) | 61,722 | 172 |

Both NBA and NHS guidelines simply require that a diagnosis of primary immunodeficiency is made by or under the supervision of a clinical immunologist. For DHBs that do not employ an immunologist, it may be difficult to see on retrospective review whether an immunologist has been involved in the diagnosis of the patient's condition or if this was simply not done. This can be seen in table 4 where DHBs with access to immunologists have much higher rates of compliance.

It has been suggested that some of the non-compliance in this group of long-term recipients may reflect the passage of time and difficulty accessing information in old notes. However, when those DHBs with 100% compliance were excluded from the analysis, a year-on-year comparison of the onset of Intragam P initiation with the level of compliance yielded no significant difference (p=0.42).

**Secondary / acquired immunodeficiency**

***Qualification and review criteria***

| Guideline | Australia | Australia | NHS |
|---|---|---|---|
| **Qualification criteria** | Diagnosis of acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation with:<br>– Recurrent or severe bacterial infection(s) and evidence of hypogammaglobulinaemia (excluding paraprotein);<br>OR<br>– Hypogammaglobulinaemia with IgG <4 g/L (excluding paraprotein) | Hypogammaglobulinaemia secondary to underlying disease or medical therapy (including haemopoietic stem cell transplantation [HCST]) with all the following:<br>– Serum IgG less than the lower limit of the reference range on two separate occasions;<br>AND<br>– Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated;<br>AND<br>At least one of the following:<br>– One invasive or life-threatening bacterial infection (e.g. pneumonia, meningitis, sepsis) in the previous year; or<br>– Clinically active bronchiectasis confirmed by radiology | Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated;<br>OR<br>Hypogammaglobulinaemia associated with NHL, age-specific serum IgG CLL, MM or other relevant B-cell malignancy reference range confirmed by haematologist; AND<br>– Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months<br>– IgG <5g/L (excluding paraprotein)<br>– Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge |
| **Exclusion criteria** | The following conditions should not be approved under this indication:<br>1.HIV in children<br>2.Transplantation-related immunomodulation<br>3.Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency | Reversible underlying cause of hypogammaglobulinaemia.<br>The following conditions should not be approved under this indication:<br>1.Acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation<br>2.HIV in children<br>3.Transplantation related immunomodulation | |
| **Review criteria** | Six-monthly review to assess clinical benefit.<br>Cessation of IVIg should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy.<br>Written confirmation from the treating physician that:<br>– an annual review has been undertaken;<br>– the patient had demonstrated clinical benefit;<br>– a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds.<br>In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit. | Six-monthly review to assess clinical benefit. Cessation of IVIg should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy.<br>Written confirmation from the treating physician that:<br>– an annual review has been undertaken;<br>– the patient had demonstrated clinical benefit;<br>– a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds.<br>In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit. | Reduction in number of infections and days in hospital |

The NBA criteria separate secondary immunodeficiency into those resulting from a haematological malignancy and/or stem cell transplant, which has an established role, and those related to other diseases or medical therapy, which has an emerging therapeutic role whereas the NHS guideline has a single category for all types of secondary immunodeficiency.

Secondary immunodeficiency accounted for 186 of the 864 (21.5%) episodes audited and for 18% of the Intragam P used at DHBs covered by the audit. The proportion of total immunoglobulin, when including subcutaneous treatment, falls to 17%. Average use of Intragam P per patient is 199g/year with a wide range (0.1 – 14.8 g/kg/year). This may reflect that Intragam P is being used acutely for specific clinical episodes or it is being trialled and patients then taken off it.

Table 5 shows data on compliance with qualification criteria. This is an area where compliance appears to be problematic for all participating DHBs. This is particularly the case when assessed against the NHS guideline.

When assessed against the Australian criteria, 22% of Intragam P issued for this indication was to patients who did not meet the criterion of recurrent infections with evidence of hypogammaglobulinaemia. 50% was to patients who did not meet the requirement for an IgG level below 4g/L. Compliance with only one of these two criteria is required. However 20% of product was used in patients that met neither criterion.

When assessed against the NHS criteria, 23% of Intragam P issued was to patients who did not have recurrent infections, 44% to patients with IgG levels 5g/L or greater and only a small minority met the requirement to demonstrate a failed response to unconjugated pneumococcal/polysaccharide vaccination.

**Table 5:** *Secondary immunodeficiency: compliance with NBA and NHS qualification criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 3,396 (62%) | 23 (56%) | 987 (18%) | 3 (7%) | 5,448 | 41 |
| Canterbury | 3,954 (67%) | 18 (67%) | 384 (6%) | 2 (7%) | 5,928 | 27 |
| Capital and Coast | 912 (11%) | 5 (14%) | 363 (4%) | 1 (3%) | 8,451 | 37 |
| Counties Manukau | 1,749 (59%) | 8 (53%) | 0 (0%) | 0 (0%) | 2,988 | 15 |
| Hawkes Bay | 852 (47%) | 2 (67%) | 0 (0%) | 0 (0%) | 1,815 | 3 |
| MidCentral | 624 (39%) | 3 (43%) | 0 (0%) | 0 (0%) | 1,608 | 7 |
| Northland | 531 (100%) | 3 (100%) | 228 (43%) | 1 (33%) | 531 | 3 |
| Southern | 2,277 (67%) | 13 (57%) | 690 (20%) | 2 (9%) | 3,405 | 23 |
| Waikato | 2,037 (29%) | 8 (27%) | 0 (0%) | 0 (0%) | 6,912 | 30 |
| Overall | 16,332 (44%) | 83 (45%) | 2,652 (7%) | 9 (5%) | 37,086 | 186 |

The low level of compliance with the qualification criteria in CCDHB merits special note. This in part relates to a specific policy of supporting allogeneic haemopoietic stem cell transplant patients (HSCT) with IVIg prophylactically i.e. without evidence of pre-existing hypogammaglobulinaemia. The NBA guideline considers use of IVIg in this setting and identifies no survival benefit evident in studies conducted post 2000. Use of IVIg post HCST with evidence of secondary immunodeficiency is however supported. The NHS guideline is silent on this topic. At least 17 of the 37 patients treated at CCDHB for secondary immunodeficiency during the audit period fall into this category. If these are excluded, then compliance with the NBA qualification criteria rises to at least 25%.

**Table 6:** *Secondary immunodeficiency: compliance with NBA and NHS review criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 4,932 (91%) | 32 (78%) | 5,448 (100%) | 41 (100%) | 5,448 | 41 |
| Canterbury | 5,268 (89%) | 25 (93%) | 5,928 (100%) | 27 (100%) | 5,928 | 27 |
| Capital and Coast | 5,112 (60%) | 25 (68%) | 4,773 (56%) | 22 (59%) | 8,451 | 37 |
| Counties Manukau | 1,917 (64%) | 11 (73%) | 2,673 (89%) | 13 (87%) | 2,988 | 15 |
| Hawkes Bay | 1,815 (100%) | 3 (100%) | 852 (47%) | 2 (67%) | 1,815 | 3 |
| MidCentral | 1,044 (65%) | 5 (71%) | 1,374 (85%) | 6 (86%) | 1,608 | 7 |
| Northland | 531 (100%) | 3 (100%) | 531 (100%) | 3 (100%) | 531 | 3 |
| Southern | 2,553 (75%) | 21 (91%) | 3,405 (100%) | 23 (100%) | 3,405 | 23 |
| Tairawhiti | 0 | 0 | 0 | 0 | 0 | 0 |
| Waikato | 2,133 (31%) | 11 (37%) | 6,378 (92%) | 28 (93%) | 6,912 | 30 |
| Overall | 25,305 (68%) | 136 (73%) | 31,362 (85%) | 165 (89%) | 37,086 | 186 |

NBA guidelines require written confirmation of a review, demonstration of clinical benefit and consideration whether a trial of cessation of IVIG would be safe. Many DHBs performed poorly here but this may reflect poor documentation rather than lack of clinical consideration (table 6).

NHS guidelines require demonstration of a reduction in the number of infections and days in hospital. This was generally performed well (table 6) but it was not possible, when reviewing the data from the audit, to easily distinguish between subjective and objective assessments by the treating clinician or auditor.

Secondary immunodeficiency was the second largest indication for Intragam P in the audit. The poor level of compliance with the qualification criteria is a concern and suggests that a more structured approach to assessment of these patients prior to commencement of treatment will be of benefit.

## Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

### *Qualification and review criteria*

| Guideline | Australia | NHS |
|---|---|---|
| **Qualification criteria** | 1. Diagnosis of CIDP verified by a neurologist;<br>AND<br>2. Significant functional impairment of activities of daily living (ADL). | Probable or definite diagnosis of CIDP by a neurologist according EFNS/ International Peripheral Nerve Society Guidelines[9];<br>AND<br>Significant functional impairment inhibiting normal daily activities. |
| **Review criteria** | IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary.<br><br>If there is no benefit after three to six courses, IVIg therapy should be abandoned.<br><br>Regular review by a neurologist is required: frequency as determined by clinical status of patient.<br><br>For stable patients on maintenance treatment, review by a neurologist is required at least annually.<br><br>**Effectiveness**<br><br>Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.<br><br>Effectiveness can be demonstrated by objective findings of either:<br><br>1. improvement in functional scores (activities of daily living — ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment or neuropathy score; or<br><br>2. stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores. | Improvement in any of the following pre-specified measures (record 3 of 5)<br><br>- MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70)<br>- INCAT sensory sum score<br>- The ONLS<br>- Up and go 10-m walk (in seconds)<br>- Other validated disability measure |

CIDP accounted for 65 of the 864 (7.5%) episodes audited and for 16% of the Intragam P used at DHBs covered by the audit. The proportion of total immunoglobulin falls to 15% when the impact of subcutaneous treatment is included. It is the largest neurological diagnosis for use of Intragam P. Average use of Intragam P is 514g per patient per year. This is the highest figure for any diagnosis with a significant total number of patients included in the audit.

Data is shown in table 7. Overall, there is reasonable compliance with the qualification criteria although with variability between DHBs, at least in part due to the small number of patients in each DHB.

**Table 7:** *CIDP: compliance with NBA and NHS qualification criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 9,069 (99%) | 18 (95%) | 9,123 (100%) | 19 (100%) | 9,123 | 19 |
| Canterbury | 6,711 (93%) | 13 (87%) | 180 (2%) | 1 (7%) | 7,245 | 15 |
| Capital and Coast | 30 (8%) | 1 (33%) | 0 (0%) | 0 (0%) | 354 | 3 |
| Counties Manukau | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 468 | 2 |
| Hawkes Bay | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 666 | 2 |
| MidCentral | 108 (6%) | 1 (20%) | 0 (0%) | 0 (0%) | 1,941 | 5 |
| Northland | 753 (53%) | 2 (50%) | 753 (53%) | 2 (50%) | 1,413 | 4 |
| Southern | 4,602 (100%) | 6 (100%) | 624 (14%) | 1 (17%) | 4,602 | 6 |
| Tairawhiti | 1,680 (100%) | 2 (100%) | 1,680 (100%) | 2 (100%) | 1,680 | 2 |
| Waikato | 3,132 (53%) | 4 (57%) | (0%) | (0%) | 5,910 | 7 |
| Overall | 26,085 (78%) | 47 (72%) | 12,360 (37%) | 25 (38%) | 33,402 | 65 |

Data on rates of compliance with review criteria are shown in table 8. Presumably because of the doses of intravenous immunoglobulin required and the long duration, both NHS and NBA guidelines are far more proscriptive of the reviews required for CIDP than for other disorders e.g. Guillain-Barré syndrome. The NBA guideline places emphasis on regular review with both guidelines recommending objective measures of effectiveness.

**Table 8:** *CIDP: compliance with NBA and NHS review criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 9,123 (100%) | 19 (100%) | 9,123 (100%) | 19 (100%) | 9,123 | 19 |
| Canterbury | 6,711 (93%) | 13 (87%) | 4,959 (68%) | 10 (67%) | 7,245 | 15 |
| Capital and Coast | 30 (8%) | 1 (33%) | 0 (0%) | 0 (0%) | 354 | 3 |
| Counties Manukau | 0 (0%) | 0 (0%) | 369 (79%) | 1 (50%) | 468 | 2 |
| Hawkes Bay | 0 (0%) | 0 (0%) | 330 (50%) | 1 (50%) | 666 | 2 |
| MidCentral | 228 (12%) | 2 (40%) | 1,941 (100%) | 5 (100%) | 1,941 | 5 |
| Northland | 753 (53%) | 2 (50%) | 849 (60%) | 3 (75%) | 1,413 | 4 |
| Southern | 4,602 (100%) | 6 (100%) | 4,602 (100%) | 6 (100%) | 4,602 | 6 |
| Tairawhiti | 1,680 (100%) | 2 (100%) | 1,680 (100%) | 2 (100%) | 1,680 | 2 |
| Waikato | 3,132 (53%) | 4 (57%) | 3,186 (54%) | 3 (43%) | 5,910 | 7 |
| Overall | 26,259 (79%) | 49 (75%) | 27,039 (81%) | 50 (77%) | 33,402 | 65 |

## Guillain-Barré Syndrome

### *Qualification and review criteria*

| Guideline | Australia | NHS |
|---|---|---|
| **Qualification criteria** | Patients with GBS (or variant) with significant disability and disease progression.<br><br>Note: Assessment by a neurologist is recommended, but not mandatory. | Diagnosis of GBS (or variant) in hospital; AND<br>Significant disability (Hughes Grade 4);<br>OR<br>Disease progression |
| **Review criteria** | Primary outcome measures: improvement in disability grade four weeks after treatment. | Record the disability grade at diagnosis |

Guillain-Barré syndrome accounted for 65 of the 864 (7.5%) episodes audited and for 6% of the Intragam P used at DHBs covered by the audit. The proportion of total immunoglobulin, when including subcutaneous treatment, is 5.7%.

Data on compliance with qualification criteria for Guillain-Barré syndrome is shown in table 9. Both guidelines require the patient to be showing significant disability. The NBA guideline does not specify what is represented by significant disability, so this is possibly an area where the auditors and neurologists had different views. The NHS criteria specify either disease progression or that the patient is bed- or chair-bound.

The range of dose size per year in grams per kilogram bodyweight was surprisingly large (0.4 – 17.4 g/kg). This suggests that some patients have a different disorder, e.g. CIDP, which has presented with features of Guillain-Barré syndrome. This makes it more difficult to provide accurate audit data for comparison but also raises the possibility that diagnoses are being carried over possibly without thinking through the implications of treatment and the guidance that guidelines can offer for different diagnoses.

**Table 9:** *Guillain-Barré syndrome: Compliance with NBA and NHS qualification criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 1,737 (100%) | 12 (100%) | 1,737 (100%) | 12 (100%) | 1,737 | 12 |
| Canterbury | 1,938 (97%) | 10 (91%) | 1,458 (73%) | 9 (82%) | 1,998 | 11 |
| Capital and Coast | 0 (0%) | 0 (0%) | 360 (49%) | 2 (50%) | 735 | 4 |
| Counties Manukau | 129 (30%) | 1 (25%) | 0 (0%) | 0 (0%) | 432 | 4 |
| Hawkes Bay | 228 (12%) | 2 (67%) | 1,740 (88%) | 1 (33%) | 1,968 | 3 |
| MidCentral | 450 (23%) | 3 (33%) | 1,350 (69%) | 7 (78%) | 1,953 | 9 |
| Northland | 816 (100%) | 5 (100%) | 816 (100%) | 5 (100%) | 816 | 5 |
| Southern | 540 (78%) | 3 (75%) | 312 (45%) | 2 (50%) | 690 | 4 |
| Tairawhiti | 510 (100%) | 2 (100%) | 510 (100%) | 2 (100%) | 510 | 2 |
| Waikato | 1,431 (93%) | 10 (91%) | 1,368 (89%) | 9 (82%) | 1,536 | 11 |
| Overall | 7,779 (63%) | 48 (74%) | 9,651 (78%) | 49 (75%) | 12,375 | 65 |

Compliance rates of DHBs with qualification criteria were most variable in the neurological disorders audited, including Guillain-Barré syndrome, although small numbers of patients per DHB may be contributing to this. Neither guideline requires the diagnosis of Guillain-Barré to be made by a neurologist.

Data on compliance with review criteria is shown in table 10. Review of patients with Guillain-Barré receiving Intragam P looks at disability grade at diagnosis (NHS) or at four weeks (NBA). The NBA

criterion is improvement in disability. This introduces the possibility that a review that did not show improvement may not have been recorded as meeting the guideline, a possible source of error only detected at the end of the audit.

**Table 10:** *Guillain-Barré syndrome: Compliance with NBA and NHS review criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 1,737 (100%) | 12 (100%) | 1,737 (100%) | 12 (100%) | 1,737 | 12 |
| Canterbury | 1,998 (100%) | 11 (100%) | 1,458 (73%) | 9 (82%) | 1,998 | 11 |
| Capital and Coast | 360 (49%) | 2 (50%) | 360 (49%) | 2 (50%) | 735 | 4 |
| Counties Manukau | 129 (30%) | 1 (25%) | 0 (0%) | 0 (0%) | 432 | 4 |
| Hawkes Bay | 228 (12%) | 2 (67%) | 1,968 (100%) | 3 (100%) | 1,968 | 3 |
| MidCentral | 1,953 (100%) | 9 (100%) | 1,788 (92%) | 8 (89%) | 1,953 | 9 |
| Northland | 816 (100%) | 5 (100%) | 816 (100%) | 5 (100%) | 816 | 5 |
| Southern | 690 (100%) | 4 (100%) | 312 (45%) | 2 (50%) | 690 | 4 |
| Tairawhiti | 510 (100%) | 2 (100%) | 510 (100%) | 2 (100%) | 510 | 2 |
| Waikato | 1,431 (93%) | 10 (91%) | 1,368 (89%) | 9 (82%) | 1,536 | 11 |
| Overall | 9,852 (80%) | 58 (89%) | 10,317 (83%) | 52 (80%) | 12,375 | 65 |

## Immune Thrombocytopenic Purpura (ITP)

### *Qualification and review criteria*

| Guideline | Australia | NHS |
|---|---|---|
| **Qualification criteria** | **1. Refractory acute ITP *on the recommendation of a haematologist***<br>– Patients qualify for initial IVIg therapy when conventional doses of corticosteroids (0.5-2.0 mg/kg prednisolone, or equivalent) have failed to improve the platelet count or stop bleeding within a clinically appropriate time frame, as assessed by a clinical haematologist. The objective of therapy is to induce a prompt increase in the platelet count (to >30x$10^9$/L) while other therapies are introduced.<br>– Patients qualify for continuing doses when splenectomy has failed or is contraindicated AND where therapy with at least one second-line agent has been unsuccessful in maintaining a platelet count >30x$10^9$/L.<br>With ongoing therapy, IVIg may be administered to achieve a platelet count >30x$10^9$/L. Further doses may be administered in responsive patients for up to 6 months (thereafter see Chronic refractory ITP). The frequency and dose should be titrated to maintain a platelet count of at least 30x$10^9$/L. The objective of therapy is to maintain a safe platelet count while other therapeutic options are explored.<br>**2. ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage**<br>IVIg therapy may be given when conventional doses of corticosteroids have failed or in conjunction with steroids when a rapid response is required.<br>**3. ITP in pregnancy**<br>– Platelets <30x$10^9$/L: IVIg therapy may be used to avoid corticosteroids, immunosuppressive agents and splenectomy. Further doses titrated to maintain a platelet count >30x$10^9$/L may be administered every three to four weeks throughout the pregnancy.<br>– Impending delivery: IVIg therapy may be used to achieve a platelet count considered safe for delivery (80–100x$10^9$/L).<br>**4. Specific circumstances**<br>– Planned surgery: IVIg may be used to achieve a platelet count considered safe for surgery. The safe threshold will vary with the nature of the surgery (Recommended platelet counts for patients without concurrent risks of bleeding: minor dental work >30x$10^9$/L, minor surgery >50x$10^9$/L, major surgery >80x$10^9$/L, major neurosurgery >100x$10^9$/L.)<br>– Severe ITP: IVIg may be used where corticosteroids and immunosuppression are contraindicated.<br>– Chronic refractory ITP unresponsive to all other available therapies: These patients may be considered for long-term maintenance therapy with IVIg, subject to regular review by a haematologist.<br>**5. HIV-associated ITP**<br>– Failure of antiretroviral therapy with platelet count <30x$10^9$/L;<br>OR<br>– Life-threatening haemorrhage secondary to thrombocytopenia. | **1. ITP, acute**<br>– If corticosteroids are contraindicated or more rapid response required;<br>– If no response to corticosteroids and other treatments contraindicated;<br>– Prior to surgery to achieve a safe platelet count;<br>– In children (<16 years) for emergency or prior to procedure likely to induce bleeding<br>**2. ITP, persistent**<br>For symptomatic cases unresponsive to all other treatments, IVIg is appropriate only as emergency management, e.g. potentially life-threatening haemorrhage and/or bleeding into a critical area<br>**3. ITP, chronic**<br>Lifelong treatment with IVIg should be considered as exceptional and alternative approaches (splenectomy) and treatments (such as rituximab, thrombopoietin receptor agonists) should be considered. |
| **Review criteria** | – In chronic refractory ITP, six-month review assessing evidence of clinical benefit;<br>– Resolution of bleeding;<br>– Increment in platelet count. | – Resolution in bleeding<br>– Increment in platelet count |

ITP accounted for 98 of the 864 (11%) patients audited and for 6% of the Intragam P used at DHBs covered by the audit. The proportion of total immunoglobulin, when including subcutaneous treatment, is 5.5%.

**Table 11:** *ITP: compliance with NBA and NHS qualification criteria*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 2,547 (99%) | 15 (94%) | 1,647 (64%) | 13 (81%) | 2,571 | 16 |
| Canterbury | 2,106 (100%) | 16 (100%) | 2,106 (100%) | 16 (100%) | 2,106 | 16 |
| Capital and Coast | 1,266 (100%) | 11 (100%) | 1,266 (100%) | 11 (100%) | 1,266 | 11 |
| Counties Manukau | 2,181 (100%) | 17 (100%) | 2,145 (98%) | 16 (94%) | 2,181 | 17 |
| Hawkes Bay | 126 (75%) | 1 (33%) | 168 (100%) | 3 (100%) | 168 | 3 |
| MidCentral | 618 (100%) | 5 (100%) | 474 (77%) | 4 (80%) | 618 | 5 |
| Northland | 336 (100%) | 1 (100%) | 336 (100%) | 1 (100%) | 336 | 1 |
| Southern | 1,119 (100%) | 9 (100%) | 939 (84%) | 8 (89%) | 1,119 | 9 |
| Tairawhiti | 15 (100%) | 1 (100%) | 15 (100%) | 1 (100%) | 15 | 1 |
| Waikato | 1,656 (94%) | 16 (84%) | 1,710 (97%) | 17 (89%) | 1,755 | 19 |
| Overall | 11,970 (99%) | 92 (94%) | 10,806 (89%) | 90 (92%) | 12,135 | 98 |

This indication gave excellent compliance with both guidelines with treatment being appropriately initiated in more than 90% of episodes. With the multiple possible indications for IVIG in ITP under both guidelines, it is not possible to comment on where improvements could take place. Two children were identified as not meeting the criteria of having evidence of bleeding, and three children for not having a platelet count < 30.

**Table 12:** *ITP: compliance with NBA and NHS review criteria*

| DHB | NBA Compliant | | NHS Compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 2,571 (100%) | 16 (100%) | 2,331 (91%) | 14 (88%) | 2,571 | 16 |
| Canterbury | 2,106 (100%) | 16 (100%) | 2,106 (100%) | 16 (100%) | 2,106 | 16 |
| Capital and Coast | 1,266 (100%) | 11 (100%) | 1,266 (100%) | 11 (100%) | 1,266 | 11 |
| Counties Manukau | 2,181 (100%) | 17 (100%) | 2,145 (98%) | 16 (94%) | 2,181 | 17 |
| Hawkes Bay | 168 (100%) | 3 (100%) | 168 (100%) | 3 (100%) | 168 | 3 |
| MidCentral | 618 (100%) | 5 (100%) | 618 (100%) | 5 (100%) | 618 | 5 |
| Northland | 336 (100%) | 1 (100%) | 336 (100%) | 1 (100%) | 336 | 1 |
| Southern | 1,119 (100%) | 9 (100%) | 1,119 (100%) | 9 (100%) | 1,119 | 9 |
| Tairawhiti | 15 (100%) | 1 (100%) | 15 (100%) | 1 (100%) | 15 | 1 |
| Waikato | 1,755 (100%) | 19 (100%) | 1,755 (100%) | 19 (100%) | 1,755 | 19 |
| Overall | 12,135 (100%) | 98 (100%) | 11,859 (98%) | 95 (97%) | 12,135 | 98 |

Compliance with review criteria is shown in table 12. Review criteria for the use of ITP are, for the most part, resolution of bleeding and increase in platelet count. Much like in Guillain-Barré syndrome, these criteria are about the patient's response not whether the clinician has assessed the patient. This introduces the possibility again that a review that did not show patient improvement may have been recorded as not meeting the guideline, a possible source of error only detected at the end of the audit.

## Conditions other than the 'Big 5'

Historically, and even in this audit, the majority of use of Intragam P is for primary and secondary immunodeficiency, Guillain-Barré syndrome, CIDP and ITP. These were therefore examined in greater detail. The multiple conditions not included within the 'Big 5' in the audit were grouped together as 'Other'. These indications are now responsible for 33% of episodes receiving treatment with Intragam P used in the participating DHBs and for 24% of total Intragam P use by grams. The individual conditions, together with the number of recipients and the amount of Intragam P used on each one annually, are included in Appendix 1. The full list of conditions identified in the two guidelines is shown in Appendix 3.

Information on numbers of patients and total grams by condition for each of the DHBs is shown in table 13.

**Table 13:** *Comparison of the 'Big 5' versus other indications*

| DHB | PID | | 2° ID | | GBS | | CIDP | | ITP | | Other* | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | g | n | g | n | g | n | g | n | g | n | g | n | g | n |
| Auckland | 23,952 | 70 | 5,448 | 41 | 1,737 | 12 | 9,123 | 19 | 2,571 | 16 | 13,179 (24%) | 99 (39%) | 56,010 | 257 |
| Canterbury | 8,043 | 22 | 5,928 | 27 | 1,998 | 11 | 7,245 | 15 | 2,106 | 16 | 6,642 (21%) | 46 (33%) | 31,995 | 141 |
| Capital and Coast | 9,948 | 24 | 8,451 | 37 | 735 | 4 | 354 | 3 | 1,266 | 11 | 9,516 (31%) | 39 (33%) | 30,522 | 119 |
| Counties Manukau | 1,086 | 7 | 2,988 | 15 | 432 | 4 | 468 | 2 | 2,181 | 17 | 5,196 (42%) | 30 (40%) | 12,351 | 75 |
| Hawkes Bay | 1,188 | 3 | 1,815 | 3 | 1,968 | 3 | 666 | 2 | 168 | 3 | 1,059 (15%) | 11 (41%) | 7,260 | 27 |
| MidCentral | 1,650 | 4 | 1,608 | 7 | 1,953 | 9 | 1,941 | 5 | 618 | 5 | 1,860 (19%) | 11 (27%) | 9,630 | 41 |
| Northland | 4,854 | 13 | 531 | 3 | 816 | 5 | 1,413 | 4 | 336 | 1 | 351 (4%) | 8 (23%) | 8,349 | 35 |
| Southern | 5,211 | 14 | 3,405 | 23 | 690 | 4 | 4,602 | 6 | 1,119 | 9 | 6,036 (29%) | 24 (30%) | 21,063 | 80 |
| Tairawhiti | 0 | 0 | 0 | 0 | 510 | 2 | 1,680 | 2 | 15 | 1 | 45 (2%) | 2 (29%) | 2,250 | 7 |
| Waikato | 5,790 | 15 | 6,912 | 30 | 1,536 | 11 | 5,910 | 7 | 1,755 | 19 | 6,459 (23%) | 27 (25%) | 28,362 | 109 |
| Overall | 61,722 | 172 | 37,086 | 186 | 12,375 | 65 | 33,402 | 65 | 12,135 | 98 | 50,343 (24%) | 297 (33%) | 207,792 | 891 |

Percentage is of overall use per DHB.
Abbreviations: PID: primary immunodeficiency, 2° ID: secondary immunodeficiency, GBS: Guillain-Barré syndrome, CIDP: chronic inflammatory demyelinating neuropathy, g: grams per annum, n: episodes

Compliance with qualification criteria for the 'other' conditions is shown in table 14. For these indications, the auditors assessed compliance against the two guidelines but the audit tool only captured whether the episode was compliant or not in terms of qualifying and reviewing. It did not collect data on compliance with the specific criteria for each indication.

**Table 14:** *Qualifying in conditions other than the 'Big 5': compliance with NBA and NHS guidelines*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 11646 (88%) | 71 (72%) | 12351 (94%) | 87 (88%) | 13179 | 99 |
| Canterbury | 5916 (89%) | 30 (65%) | 5682 (86%) | 39 (85%) | 6642 | 46 |
| Capital and Coast | 8463 (89%) | 26 (67%) | 7377 (78%) | 28 (72%) | 9516 | 39 |
| Counties Manukau | 4566 (88%) | 28 (93%) | 4491 (86%) | 28 (93%) | 5196 | 30 |
| Hawkes Bay | 636 (60%) | 7 (64%) | 525 (50%) | 7 (64%) | 1059 | 11 |
| MidCentral | 1815 (98%) | 8 (73%) | 1020 (55%) | 10 (91%) | 1860 | 11 |
| Northland | 348 (99%) | 7 (88%) | 165 (47%) | 7 (88%) | 351 | 8 |
| Southern | 5127 (85%) | 16 (67%) | 4683 (78%) | 14 (58%) | 6036 | 24 |
| Tairawhiti | 45 (100%) | 2 (100%) | 30 (67%) | 1 (50%) | 45 | 2 |
| Waikato | 5673 (88%) | 24 (89%) | 5145 (80%) | 21 (78%) | 6459 | 27 |
| Overall | 44235 (88%) | 219 (74%) | 41469 (82%) | 242 (81%) | 50343 | 297 |

There were a number of patients with conditions that are only in in one of the guidelines. All conditions were considered as 'non-compliant' with the guideline in which the condition was not listed for the purposes of the audit. This includes the use of IVIg for post-exposure prophylaxis for varicella zoster when intramuscular injection is inappropriate or undesirable; and use of IVIg in the management of clinical tetanus. NZBS believes use of Intragam P is appropriate for this situation and uses information on specific potency for individual antibodies in each batch of the product when recommending use in these settings. The level of compliance with qualification criteria for these 'other' indications would increase if the impact of the use of Intragam P as a source of specific antibodies were excluded.

Patient review was similarly assessed as simply whether it met the guidelines or not. Overall compliance was similar to that for the 'big 5 'indications (table 15).

**Table 15:** *Reviewing conditions other than the 'Big 5': compliance with NBA and NHS guidelines*

| DHB | NBA compliant | | NHS compliant | | Overall use | |
|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | grams | patients |
| Auckland | 11382 (86%) | 69 (70%) | 12351 (94%) | 87 (88%) | 13179 | 99 |
| Canterbury | 5994 (90%) | 29 (63%) | 5505 (83%) | 26 (57%) | 6642 | 46 |
| Capital and Coast | 7044 (74%) | 17 (44%) | 5862 (62%) | 18 (46%) | 9516 | 39 |
| Counties Manukau | 4530 (87%) | 27 (90%) | 4815 (93%) | 28 (93%) | 5196 | 30 |
| Hawkes Bay | 621 (59%) | 6 (55%) | 642 (61%) | 8 (73%) | 1059 | 11 |
| MidCentral | 1815 (98%) | 8 (73%) | 1821 (98%) | 9 (82%) | 1860 | 11 |
| Northland | 348 (99%) | 7 (88%) | 165 (47%) | 7 (88%) | 351 | 8 |
| Southern | 5070 (84%) | 12 (50%) | 4944 (82%) | 14 (58%) | 6036 | 24 |
| Tairawhiti | 45 (100%) | 2 (100%) | 45 (100%) | 2 (100%) | 45 | 2 |
| Waikato | 5283 (82%) | 23 (85%) | 5406 (84%) | 22 (81%) | 6459 | 27 |
| Overall | 42132 (84%) | 200 (67%) | 41556 (83%) | 221 (74%) | 50343 | 297 |

There were also eight patients for whom pertinent clinical records could not be found (table 16).

**Table 16:** *Episodes where no records could be found with percentages of each DHB's total use and number of patients*

| DHB | No records found | | Overall use | |
|---|---|---|---|---|
| | grams | patients | grams | patients |
| Auckland | 0 (0.0%) | 0 (0.0%) | 56,010 | 257 |
| Canterbury | 33 (0.1%) | 4 (2.8%) | 31,995 | 141 |
| Capital and Coast | 252 (0.8%) | 1 (0.8%) | 30,522 | 119 |
| Counties Manukau | 0 (0.0%) | 0 (0.0%) | 12,351 | 75 |
| Hawkes Bay | 396 (5.5%) | 2 (7.4%) | 7,260 | 27 |
| MidCentral | 0 (0.0%) | 0 (0.0%) | 9,630 | 41 |
| Northland | 48 (0.6%) | 1 (2.9%) | 8,349 | 35 |
| Southern | 0 (0.0%) | 0 (0.0%) | 21,063 | 80 |
| Tairawhiti | 0 (0.0%) | 0 (0.0%) | 2,250 | 7 |
| Waikato | 0 (0.0%) | 0 (0.0%) | 28,362 | 109 |
| Overall | 729 (0.4%) | 8 (0.9%) | 207,792 | 891 |

## Usage per patient and high use patients

In the 2005 audit, 23 high volume Intragam P recipients were found to account for 19% of Intragam P use. This was defined as more than 800g or more than 12g/kg over six months (the duration of the audit). A similar analysis was undertaken for the current audit. Using the same criteria, extrapolated to a year, i.e. 24g/kg/pa, identified only seven patients accounting for only 5% of total Intragam P use.

The 23 patients in 2005 represented 3% of total patients evaluated. If a 3% patient figure is used to define 'high user' in this audit then the cut-off levels are 890g and 12.5g/kg per annum. Figures 3 and 4 show information on grams per year by patient and grams/kg by patient.

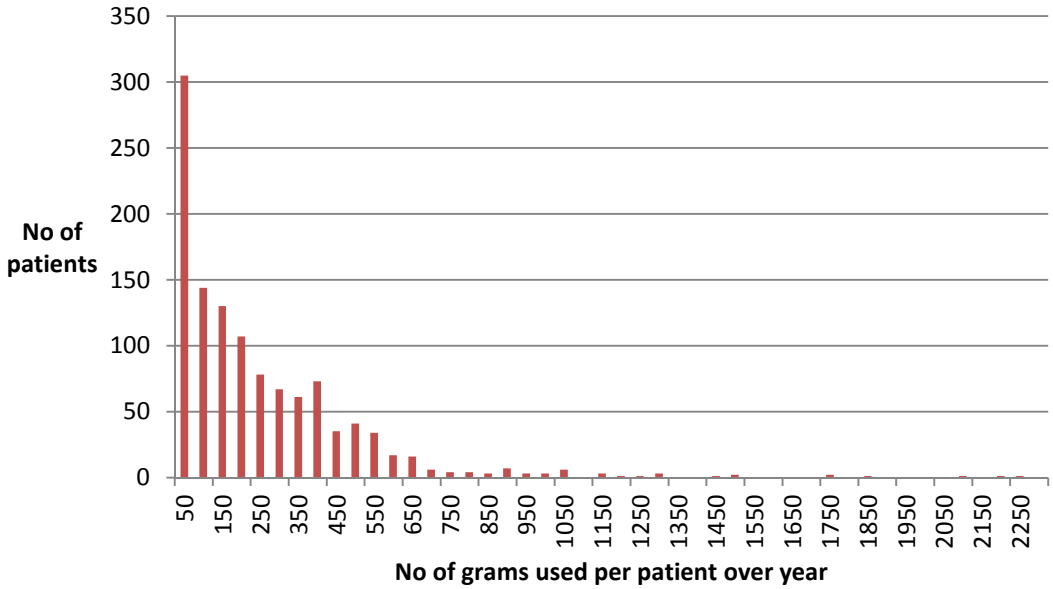


**Figure 3:** *Annual dose per patient vs number of patients nationally*

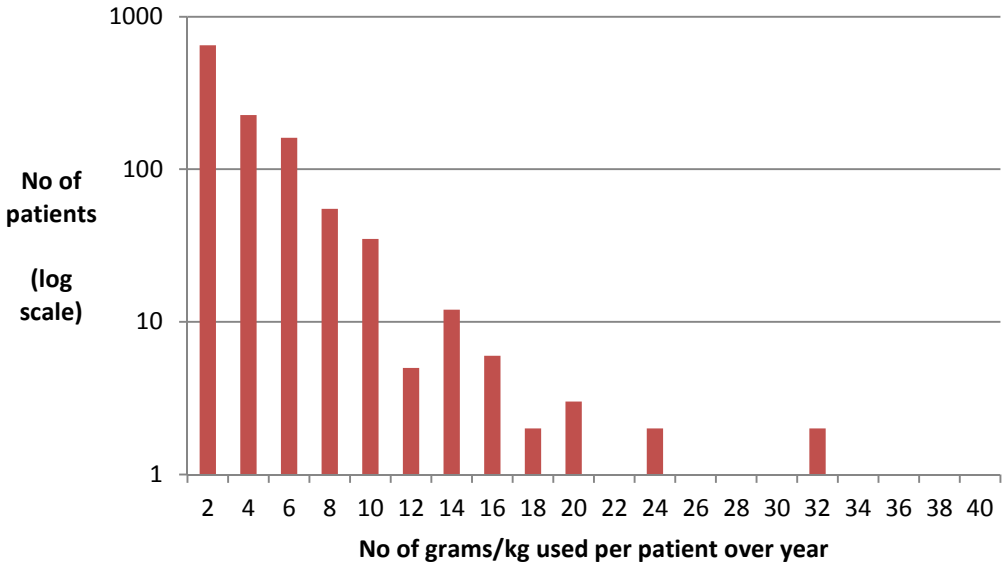


**Figure 4:** *Annual dose in grams per kilogram bodyweight per patient vs number of patients with known weights in audited hospitals*

Table 17 shows the distribution of 'high users' using the cut-offs of 890g and 12.5g/kg per annum. These account for 18% of grams used in 4% of recipients. It is unclear whether the lower than extrapolated cut-offs when compared to the 2005 audit represents a true reduction in high volume use or whether it reflects that few patients need more than 800g or 12g/kg over six months or a year. A list of indications, dose and dose per kilogram for high volume recipients is provided in appendix 2. These observations reinforce the importance of titrating the dose of IVIg to achieve maximum clinical benefit at lowest dose.

It is reassuring to see that almost all of the prescriptions and reviews for these high users met one or both guidelines (table 17). Compared with the previous audit, the diagnosis with the largest volume of use amongst high volume recipients is now CIDP (14,643g), previously in fourth place. The next closest indication is multifocal motor neuropathy with 3,144g used.

**Table 17:** *patients using > 890g and/or >12.5g/kg per annum*

| DHB | High users | | Overall use | | NBA | | NHS | |
|---|---|---|---|---|---|---|---|---|
| | grams | patients | grams | patients | qualify | review | qualify | review |
| Auckland | 9,645 (17%) | 12 (5%) | 56,010 | 257 | 100% | 100% | 93% | 100% |
| Canterbury | 5,340 (17%) | 4 (3%) | 31,995 | 141 | 100% | 100% | 100% | 100% |
| Capital and Coast | 7,020 (23%) | 6 (5%) | 30,522 | 119 | 100% | 100% | 100% | 100% |
| Counties Manukau | 1,140 (9%) | 1 (1%) | 12,351 | 75 | 100% | 100% | 100% | 100% |
| Hawkes Bay | 2,703 (37%) | 2 (7%) | 7,260 | 27 | 64% | 100% | 64% | 64% |
| MidCentral | 1,980 (21%) | 2 (5%) | 9,630 | 41 | 100% | 42% | 58% | 100% |
| Northland | 264 (3%) | 1 (3%) | 8,349 | 35 | 100% | 100% | 100% | 100% |
| Southern | 3,852 (18%) | 4 (5%) | 21,063 | 80 | 100% | 100% | 100% | 100% |
| Tairawhiti | 1,500 (67%) | 1 (14%) | 2,250 | 7 | 100% | 100% | 100% | 100% |
| Waikato | 4,509 (16%) | 3 (3%) | 28,362 | 109 | 100% | 52% | 59% | 59% |
| Grand Total | 37,953 (18%) | 36 (4%) | 207,792 | 891 | 97% | 97% | 89% | 93% |

## Blood groups

Haemolysis in non-group-O recipients is a well described phenomenon in recipients of intravenous immunoglobulin, especially at high doses, due to the presence of anti-A and anti-B from plasma donors. The prescriber's information sheet provided with Intragam P identifies this risk and recommends that patients receiving high dose IVIG (>0.4g/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. 13% of all recipients and 22% of those receiving a dose of more than 1g/kg did not have an ABO group on record at blood bank prior to the onset of the infusion (table 18). A subsequent study will look retrospectively at the incidence of haemolysis in recipients of Intragam P.

**Table 18:** *Blood group testing in relation to the onset of Intragam P treatment*

| DHB | No blood group on record | Blood group tested after initiation | Blood group present on initiation | No blood group on initiation of high dose therapy (>1g/kg) |
|---|---|---|---|---|
| Auckland | 9% (23) | 4% (11) | 87% (234) | 9% (4) |
| Canterbury | 11% (17) | 7% (11) | 82% (124) | 39% (15) |
| Capital and Coast | 0% (0) | 0% (0) | 100% (119) | 0% (0) |
| Counties Manukau | 15% (12) | 9% (7) | 77% (63) | 56% (9) |
| Hawkes Bay | 30% (8) | 0% (0) | 70% (19) | 50% (2) |
| MidCentral | 9% (4) | 5% (2) | 86% (37) | 31% (4) |
| Northland | 28% (10) | 3% (1) | 69% (25) | 56% (5) |
| Southern | 11% (9) | 6% (5) | 84% (71) | 18% (4) |
| Tairawhiti | 50% (4) | 13% (1) | 38% (3) | 100% (2) |
| Waikato | 1% (1) | 1% (1) | 98% (108) | 0% (0) |
| Overall | 9% (88) | 4% (39) | 86% (803) | 22% (45) |

## Use by clinical discipline

An alternative way to look at Intragam P use is to group indications by clinical discipline (classification shown in Appendix 3). Data on the 883 evaluable patient episodes is provided in tables 19 and 20.

**Table 19:** *Compliance with NBA guidelines by clinical discipline*

| Qualifies | Cardiac | Derm | Gynae | Haem | Immunol | Infectious | Multi-system | Neuro | Ophth | Renal | Resp | Unlisted | Overall Compliance | Overall use |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Auckland | 942 (100%) | 72 (30%) | | 8,238 (92%) | 25,674 (99%) | 54 (27%) | 3,120 (100%) | 15,168 (95%) | 408 (100%) | 36 (100%) | | 0 (0%) | 53,712 (96%) | 56,010 |
| Canterbury | 459 (58%) | 189 (100%) | | 9,873 (87%) | 8,043 (100%) | 3 (1%) | | 11,076 (99%) | | | | 0 (0%) | 29,643 (93%) | 31,962 |
| Capital and Coast | 483 (100%) | | 0 (0%) | 5,178 (49%) | 10,455 (89%) | 0 (0%) | | 6,321 (92%) | | | 66 (100%) | 0 (0%) | 22,503 (74%) | 30,270 |
| Counties Manukau | 258 (100%) | 1,986 (100%) | | 5,655 (99%) | 1,227 (59%) | 582 (100%) | 120 (100%) | 1,611 (100%) | | | | | 11,439 (93%) | 12,351 |
| Hawkes Bay | 30 (100%) | | | 978 (49%) | 972 (82%) | 3 (25%) | | 3,132 (100%) | | 105 (100%) | | 0 (0%) | 5,220 (76%) | 6,864 |
| MidCentral | 57 (100%) | | | 1,512 (68%) | 1,650 (100%) | 0 (0%) | | 5,646 (100%) | | | | | 8,865 (92%) | 9,630 |
| Northland | 108 (100%) | | | 873 (100%) | 4,386 (90%) | 0 (0%) | 48 (100%) | 1,755 (73%) | | | | | 7,170 (86%) | 8,301 |
| Southern | 126 (100%) | | | 4,683 (99%) | 1,851 (33%) | | | 9,558 (98%) | | 264 (100%) | | 0 (0%) | 16,482 (78%) | 21,063 |
| Tairawhiti | 45 (100%) | | | 15 (100%) | | | | 2,190 (100%) | | | | | 2,250 (100%) | 2,250 |
| Waikato | 168 (100%) | 12 (2%) | | 8,793 (99%) | 4,425 (67%) | 0 (0%) | 48 (100%) | 11,868 (100%) | | | | | 25,314 (89%) | 28,362 |
| Overall Compliance | 2,676 (89%) | 2,259 (70%) | 0 (0%) | 45,798 (83%) | 58,683 (87%) | 642 (50%) | 3,336 (100%) | 68,325 (97%) | 408 (100%) | 405 (100%) | 66 (100%) | 0 (0%) | 182,598 (88%) | 207,063 |

| Meets review | Cardiac | Derm | Gynae | Haem | Immunol | Infectious | Multi-system | Neuro | Ophth | Renal | Resp | Unlisted | Overall Compliance | Overall use |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Auckland | 942 (100%) | 72 (30%) | | 8,487 (94%) | 25,674 (99%) | 54 (27%) | 3,120 (100%) | 14,904 (93%) | 408 (100%) | 36 (100%) | | 0 (0%) | 53,697 (96%) | 56,010 |
| Canterbury | 798 (100%) | 189 (100%) | | 10,665 (94%) | 8,043 (100%) | 126 (54%) | | 10,299 (92%) | | | | 0 (0%) | 30,120 (94%) | 31,962 |
| Capital and Coast | 99 (20%) | | 0 (0%) | 6,384 (60%) | 11,391 (97%) | 0 (0%) | | 5,820 (85%) | | | 66 (100%) | 0 (0%) | 23,760 (78%) | 30,270 |
| Counties Manukau | 222 (86%) | 1,986 (100%) | | 4,656 (81%) | 1,437 (70%) | 582 (100%) | 120 (100%) | 840 (52%) | | | | | 9,843 (80%) | 12,351 |
| Hawkes Bay | 30 (100%) | | | 1,983 (100%) | 1,188 (100%) | 3 (25%) | | 711 (23%) | | 105 (100%) | | 0 (0%) | 4,020 (59%) | 6,864 |
| MidCentral | 57 (100%) | | | 1,668 (75%) | 1,650 (100%) | 0 (0%) | | 3,933 (70%) | | | | | 7,308 (76%) | 9,630 |
| Northland | 108 (100%) | | | 873 (100%) | 4,854 (100%) | 0 (0%) | 48 (100%) | 1,755 (73%) | | | | | 7,638 (92%) | 8,301 |
| Southern | 0 (0%) | | | 3,852 (82%) | 5,619 (99%) | | | 9,774 (100%) | | 0 (0%) | | 0 (0%) | 19,245 (91%) | 21,063 |
| Tairawhiti | 45 (100%) | | | 15 (100%) | | | | 2,190 (100%) | | | | | 2,250 (100%) | 2,250 |
| Waikato | 168 (100%) | 12 (2%) | | 4,113 (46%) | 6,588 (100%) | 0 (0%) | 48 (100%) | 8,595 (72%) | | | | | 19,524 (69%) | 28,362 |
| Overall Compliance | 2,469 (82%) | 2,259 (70%) | 0 (0%) | 42,696 (77%) | 66,444 (98%) | 765 (60%) | 3,336 (100%) | 58,821 (83%) | 408 (100%) | 141 (35%) | 66 (100%) | 0 (0%) | 177,405 (86%) | 207,063 |

**Table 20:** *Compliance with NHS guidelines by clinical discipline*

| Qualifies | Cardiac | Derm | Gynae | Haem | Immunol | Infectious | Multi-system | Neuro | Ophth | Renal | Resp | Unlisted | Overall Compliance | Overall use |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Auckland | 867 (92%) | 240 (100%) | | 3,153 (35%) | 25,914 (100%) | 201 (100%) | 3,120 (100%) | 15,990 (100%) | 408 (100%) | 0 (0%) | | 0 (0%) | 49,893 (89%) | 56,010 |
| Canterbury | 408 (51%) | 189 (100%) | | 5,862 (51%) | 8,043 (100%) | 108 (46%) | | 9,678 (86%) | | | | 0 (0%) | 24,288 (76%) | 31,962 |
| Capital and Coast | 483 (100%) | | 0 (0%) | 2,544 (24%) | 9,798 (83%) | 147 (77%) | | 6,546 (96%) | | | 66 (100%) | 0 (0%) | 19,584 (65%) | 30,270 |
| Counties Manukau | 258 (100%) | 1,986 (100%) | | 2,397 (42%) | 2,064 (100%) | 222 (38%) | 120 (100%) | 1,611 (100%) | | | | | 8,658 (70%) | 12,351 |
| Hawkes Bay | 30 (100%) | | | 168 (8%) | 1,188 (100%) | 12 (100%) | | 2,709 (86%) | | 0 (0%) | | 0 (0%) | 4,107 (60%) | 6,864 |
| MidCentral | 57 (100%) | | | 480 (22%) | 1,650 (100%) | 45 (100%) | | 4,434 (79%) | | | | | 6,666 (69%) | 9,630 |
| Northland | 108 (100%) | | | 570 (65%) | 4,386 (90%) | 3 (100%) | 48 (100%) | 1,569 (65%) | | | | | 6,684 (81%) | 8,301 |
| Southern | 126 (100%) | | | 1,812 (38%) | 1,851 (33%) | | | 9,378 (96%) | | 0 (0%) | | 0 (0%) | 13,167 (63%) | 21,063 |
| Tairawhiti | 30 (67%) | | | 15 (100%) | | | | 2,190 (100%) | | | | | 2,235 (99%) | 2,250 |
| Waikato | 168 (100%) | 12 (2%) | | 1,737 (20%) | 3,654 (55%) | 0 (0%) | 48 (100%) | 9,432 (79%) | | | | | 15,051 (53%) | 28,362 |
| Overall Compliance | 2,535 (84%) | 2,427 (76%) | 0 (0%) | 18,738 (34%) | 58,548 (86%) | 738 (58%) | 3,336 (100%) | 63,537 (90%) | 408 (100%) | 0 (0%) | 66 (100%) | 0 (0%) | 150,333 (73%) | 207,063 |

| Meets review | Cardiac | Derm | Gynae | Haem | Immunol | Infectious | Multi-system | Neuro | Ophth | Renal | Resp | Unlisted | Overall Compliance | Overall use |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Auckland | 867 (92%) | 240 (100%) | | 8,190 (91%) | 25,914 (100%) | 201 (100%) | 3,120 (100%) | 15,990 (100%) | 408 (100%) | 0 (0%) | | 0 (0%) | 54,930 (98%) | 56,010 |
| Canterbury | 408 (51%) | 189 (100%) | | 11,406 (100%) | 8,043 (100%) | 126 (54%) | | 7,917 (71%) | | | | 0 (0%) | 28,089 (88%) | 31,962 |
| Capital and Coast | 111 (23%) | | 0 (0%) | 10,629 (100%) | 9,588 (82%) | 138 (72%) | | 4,995 (73%) | | | 66 (100%) | 0 (0%) | 25,527 (84%) | 30,270 |
| Counties Manukau | 222 (86%) | 1,986 (100%) | | 5,349 (93%) | 2,064 (100%) | 582 (100%) | 120 (100%) | 1,080 (67%) | | | | | 11,403 (92%) | 12,351 |
| Hawkes Bay | 30 (100%) | | | 1,983 (100%) | 1,188 (100%) | 9 (75%) | | 2,796 (89%) | | 105 (100%) | | 0 (0%) | 6,111 (89%) | 6,864 |
| MidCentral | 57 (100%) | | | 2,232 (100%) | 1,650 (100%) | 6 (13%) | | 5,481 (97%) | | | | | 9,426 (98%) | 9,630 |
| Northland | 108 (100%) | | | 873 (100%) | 4,386 (90%) | 3 (100%) | 48 (100%) | 1,665 (69%) | | | | | 7,083 (85%) | 8,301 |
| Southern | 126 (100%) | | | 4,704 (100%) | 1,851 (33%) | | | 9,000 (92%) | | 264 (100%) | | 0 (0%) | 15,945 (76%) | 21,063 |
| Tairawhiti | 45 (100%) | | | 15 (100%) | | | | 2,190 (100%) | | | | | 2,250 (100%) | 2,250 |
| Waikato | 168 (100%) | 660 (83%) | | 8,694 (98%) | 3,654 (55%) | 3 (100%) | 48 (100%) | 8,256 (70%) | | | | | 21,483 (76%) | 28,362 |
| Overall Compliance | 2,142 (71%) | 3,075 (96%) | 0 (0%) | 54,075 (97%) | 58,338 (86%) | 1,068 (84%) | 3,336 (100%) | 59,370 (84%) | 408 (100%) | 369 (91%) | 66 (100%) | 0 (0%) | 182,247 (88%) | 207,063 |
| | | | | | | | | | | | | | | |
| Overall Use | 3015 | 3210 | 84 | 55473 | 67800 | 1272 | 3336 | 70701 | 408 | 405 | 66 | 1293 | | 207063 |

## DISCUSSION

This audit evaluated the use of Intragam P against guidelines developed, and in use, in Australia and the United Kingdom, in ten DHBs over a period of a year between July 2012 and June 2013. 891 qualifying episodes were identified of which 883 were fully evaluable. The audit was retrospective in nature. This introduced a number of limitations to the analysis of the data. Overall however the information identified within the audit provides an overview of how Intragam P was used during the period.

When assessed against the NBA guidelines, 76% of all evaluable patient episodes (88% of total grams issued) met the qualification criteria and 76% the review criteria (86% total grams). Correspondingly, 76% of patient episodes (73% of total grams issued) met the NHS qualifying criteria and 75% met the review criteria (88% of total grams issued).

This audit has shown reasonable compliance with guidelines for many of the indications for which it was prescribed. Nevertheless, 12% of total grams of Intragam P used during the period of the audit may not have been appropriately prescribed, using the Australian National Blood Authority (NBA) guidelines or as much as 27% using the British National Health Service (NHS) guidelines. However between 86% and 88% appears to have been appropriately reviewed based on the NBA and NHS guidelines. These percentages need to be considered in the light of the limitations of the audit described above.

The most noticeable area for problems with compliance with the guidelines appears to be secondary immunodeficiency. With 18% of Intragam P used for this indication, the opportunity to refine use would seem to be evident. This is particularly pertinent in an indication where there is relatively poor data supporting its use[10]. One estimate has suggested that replacement therapy in secondary immunodeficiency yielded only 0.8 quality adjusted days per year per recipient at a cost of $6 million per quality adjusted life year[11].

The data on the distribution of intravenous immunoglobulin amongst different indications is similar to that of other audits[23,11-13]. Although the rankings varied, secondary immunodeficiency and ITP were in the top five of all these audits. Primary immunodeficiency and CIDP were in the top five of three audits with Guillain-Barré syndrome and multifocal motor neuropathy in the top five of two audits. The relative predominance of conditions was noted to vary based on referral patterns to the institutions audited. This can be seen to a certain extent in table 13 where different indications contribute significantly differently across the DHBs audited.

This audit raises some interesting issues around the use of intravenous immunoglobulin. Both internationally and locally, the demand for intravenous immunoglobulin has risen significantly year on year for decades but with great variation in actual demand per capita in different countries. In international terms, New Zealand is an intermediate level user of intravenous immunoglobulin, comparable with the United Kingdom, Switzerland and Italy, but ahead of countries such as Germany and Japan[15]. Australia has led the world in consumption, currently running at over 172g per 1000 population in 2014 and continues to rise at a rate of approximately 11% per year[5]. This compares with New Zealand's current rate of 73g per 1000 population.

Although the demand for plasma has at times out-stripped supply by up to 20-30%, notably in the late 1990's[12], commercial plasma fractionators have responded and now have sufficient capacity and ability to respond to increasing demands at least for several years ahead[14]. Nevertheless, this leaves this scarce and expensive resource in the hands of a very small number of firms with consequent supply risks as seen in the 1990's where regulatory issues restricted supply by certain companies[12].

One of the issues that has been debated in terms of controlling intravenous immunoglobulin use has been dosing in overweight recipients. More than 30% of people living in New Zealand are obese[15] so savings on treating patients based on lean body weight could be significant. Although this audit was not able to look at the body mass index (BMI) of recipients, where a weight was known, 25% weighed 80kg or more, suggesting that this is indeed an area for some potential

savings. A report from the USA found a 6% saving in intravenous immunoglobulin use by applying a lean body weight formula[13] but New Zealand might not expect to gain as much as this practice is already in place in some areas. Both the Australian and NHS guidelines discuss the use of 'lean body weight' for this purpose. The Australian Guidelines identify that '*while there is some evidence for the use of dosing based on lean body weight, further research is required.*' The NHS guidelines identify that '*there is considerable interest in the use of ideal body weight-adjusted dosing of immunoglobulin, based on the view that drugs with a narrow therapeutic index are usually dose-adjusted by surface area or another formula to allow for the poorly perfused excess adipose tissue. The concept of using biological agents at their lowest effective dose is logical and may also contribute to minimisation of side-effects, some of which may be dose related. This would also save significant quantities of immunoglobulin*.' They go on to state '*there is a very limited evidence base, which is too weak to allow a firm recommendation, but there are some reports supporting this approach.'* At this stage there is no real data on the impact of this approach in New Zealand.

A new issue that may increase pressure on intravenous immunoglobulin use is that of immunodeficiency consequent on rituximab use. Rituximab is most often used in patients with B cell malignancies, where immunodeficiency secondary to chemotherapy might be expected. The use of rituximab in autoimmune disorders has highlighted how repeated courses of rituximab can lead to such severe immunodeficiency that intravenous immunoglobulin replacement therapy becomes necessary[16]. In a study at the Memorial Sloan-Kettering Cancer Centre[17], 23% of patients with Non-Hodgkin lymphoma with initially normal serum IgG levels treated with rituximab developed hypogammaglobulinaemia with IgG levels less than 4g/L. 6.6% of patients went on to require intravenous immunoglobulin. This study reiterated that the incidence of hypogammaglobulinaemia was worse with repeated courses of rituximab. However it also showed that the mean time to onset of hypogammaglobulinaemia in patients with previously normal IgG levels was 1.4 years, suggesting that the connection between low IgG levels and rituximab may not be obvious to clinicians treating patients with multiple agents.

One of the recognised complications of intravenous immunoglobulin is haemolysis with a mean fall in haemoglobin of 43g/L when it occurs[18]. This is likely under-recognised and under-reported in New Zealand as, when followed prospectively, as many as one in twenty patients develop haemolysis[19]. Because the majority of haemolysis is due to anti-A and anti-B antibodies in the intravenous immunoglobulin, it is recommended that clinicians monitor non-group-O patients for signs of haemolysis. It was therefore gratifying to see that 86% of patients had a blood group tested by a blood bank prior to commencing Intragam P. This is a substantial improvement on the 38% found in the previous audit. However, because high dose treatment is particularly associated with haemolysis[20], it is still of concern that 22% of patients receiving more than 1g/kg did not have a blood group at the onset of treatment. A study currently being planned by NZBS will look retrospectively at the incidence of haemolysis in new patients in this audit receiving more than 1g/kg/month.

This audit has shown some areas for improvement and highlighted how managing the rising demand for intravenous immunoglobulin, both locally and internationally, is a problem that needs solving. A Canadian study[2] looked at the impact of providing reports, pre-printed forms with dosing schedules, and feedback on trough levels for patients on replacement therapy. While other provinces saw a 9% increase in intravenous immunoglobulin use, the provinces taking part in this study saw a 7% decrease.

NZBS utilises a pre-approval process for accessing Intragam P. This is however used inconsistently by different DHBs. Requests for the product are assessed against the guidelines but the strict qualification criteria are not currently enforced. A number of DHBs have indicated a desire to move to a more formal process for accessing these products. Tools for simplifying peer or expert review at the initiation and review of Intragam P treatment can be expected to improve compliance. This would also assist the smaller DHBs whose use appears to be climbing at a faster rate than the larger DHBs, as well as larger DHBs who see a large financial outlay in Intragam P. Introduction of this type of process will require agreement with participating DHBs. This would require identification of a specific set of qualification and review criteria and a process for review of

requests falling outside of the criteria. The Australian guidelines will likely be most appropriate given the close clinical contacts between New Zealand and Australia. NZBS is currently developing an electronic approval process that will provide better information and enable easier reporting to DHBs and this could form the first step in the development of a broader governance process.

In summary, this audit has provided insights into the use of Intragam P and compliance with two international guidelines. While there is still room for improvement, progress has been made compared to the previous audit. The time has now come when serious consideration should be given to proactively capturing indications for and review of Intragam P use and providing feedback to clinicians and DHBs in a more accurate and timely manner.

## ACKNOWLEDGMENTS

This audit was funded by NZBS and Counties Manukau DHB in employing the transfusion nurse specialists, transfusion medicine specialist and data analyst who captured the data and prepared the report. The authors are grateful for the assistance of Carolyn Jeffrey, NZBS data analyst, for providing data extracts from eProgesa to support this audit.

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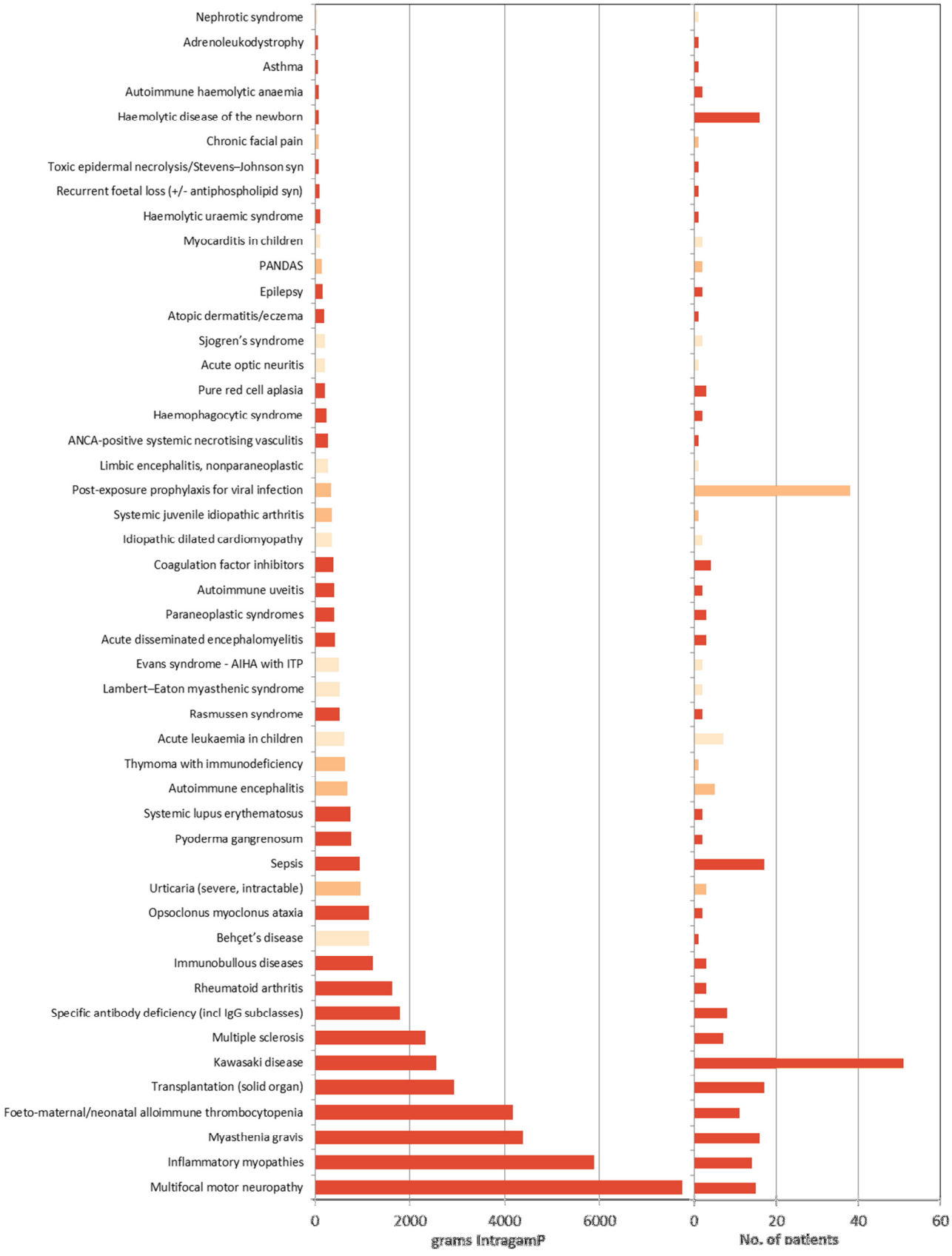
## APPENDICES

## Appendix 1: Use of Intragam P per condition




The indications are categorised into whether they are reflected in both guidelines (dark), NHS only (medium) or NBA only (light).

## Appendix 2: High volume recipients

| DHB | indication | total dose (grams) | weight (kg) | dose (g/kg) |
|---|---|---|---|---|
| Auckland | Chronic inflammatory demyelinating polyneuropathy | 1017 | 56 | 18.2 |
| Auckland | Chronic inflammatory demyelinating polyneuropathy | 1032 | 60 | 17.3 |
| Auckland | Chronic inflammatory demyelinating polyneuropathy | 1272 | 80 | 15.9 |
| Auckland | Guillain-Barré syndrome | 588 | 34 | 17.4 |
| Auckland | Immune thrombocytopenic purpura | 684 | 50 | 13.7 |
| Auckland | Inflammatory myopathies | 990 | 99 | 10.0 |
| Auckland | Opsoclonus myoclonus ataxia | 618 | 17 | 36.4 |
| Auckland | Primary immunodeficiency | 1020 | 78 | 13.2 |
| Auckland | Rheumatoid arthritis | 576 | 45 | 12.7 |
| Auckland | Systemic juvenile idiopathic arthritis | 348 | 24 | 14.3 |
| Auckland | Transplantation (solid organ) | 225 | 7 | 30.4 |
| Auckland | Transplantation (solid organ) | 1275 | 56 | 22.7 |
| Canterbury | Acquired (secondary) antibody deficiency | 900 | 61 | 14.8 |
| Canterbury | Chronic inflammatory demyelinating polyneuropathy | 948 | - | 0.0 |
| Canterbury | Chronic inflammatory demyelinating polyneuropathy | 1440 | 96 | 15.0 |
| Canterbury | Foeto-maternal/neonatal alloimmune thrombocytopenia | 2052 | 74 | 27.9 |
| Capital and Coast | Behçet's disease | 1131 | 110 | 10.3 |
| Capital and Coast | Foeto-maternal/neonatal alloimmune thrombocytopenia | 897 | 70 | 12.8 |
| Capital and Coast | Inflammatory myopathies | 978 | 96 | 10.2 |
| Capital and Coast | Multifocal motor neuropathy | 2226 | 70 | 31.8 |
| Capital and Coast | Primary immunodeficiency | 864 | 62 | 13.9 |
| Capital and Coast | Primary immunodeficiency | 924 | 103 | 9.0 |
| Counties Manukau | Immunobullous diseases | 1140 | 58 | 19.7 |
| Hawkes Bay | Acquired (secondary) antibody deficiency | 963 | 79 | 12.2 |
| Hawkes Bay | Guillain-Barré syndrome | 1740 | 179 | 9.7 |
| MidCentral | Chronic inflammatory demyelinating polyneuropathy | 1140 | 92 | 12.4 |
| MidCentral | Multiple sclerosis | 840 | 60 | 14.0 |
| Northland | Chronic inflammatory demyelinating polyneuropathy | 264 | 20 | 13.2 |
| Southern | Chronic inflammatory demyelinating polyneuropathy | 1014 | 87 | 11.7 |
| Southern | Chronic inflammatory demyelinating polyneuropathy | 1020 | 80 | 12.8 |
| Southern | Inflammatory myopathies | 900 | 74 | 12.2 |
| Southern | Multifocal motor neuropathy | 918 | 64 | 14.3 |
| Tairawhiti | Chronic inflammatory demyelinating polyneuropathy | 1500 | 82 | 18.3 |
| Waikato | Chronic inflammatory demyelinating polyneuropathy | 1836 | 122 | 15.0 |
| Waikato | Chronic inflammatory demyelinating polyneuropathy | 2160 | 90 | 24.0 |
| Waikato | Opsoclonus myoclonus ataxia | 513 | 24 | 21.8 |

## Appendix 3: Conditions listed as 'Other'

**Cardiac**
Acute rheumatic fever
Autoimmune congenital heart block
Cardiac surgery with bypass - prophylaxis
Congestive cardiac failure
Idiopathic dilated cardiomyopathy
Kawasaki disease
Myocarditis in children

**Dermatology**
Atopic dermatitis/eczema
Bullous pemphigoid
Cicatricial pemphigoid
Epidermolysis bullosa acquisita
Henoch–Schonlein purpura
Immunobullous diseases
Linear IgA disease
Pemphigus foliaceus
Pemphigus vulgaris
Pyoderma gangrenosum
Toxic epidermal necrolysis/Stevens–Johnson
Toxic shock syndrome
Urticaria (severe, intractable)

**Gastroenterology**
Crohn's disease
Ulcerative colitis

**Gynaecology**
Female infertility
Recurrent foetal loss (±antiphospholipid syndrome)

**Haematology**
Acute leukaemia in children
Amegakaryocytic thrombocytopenia
Antiphospholipid syndrome
Aplastic anaemia/pancytopenia
Autoimmune haemolytic anaemia
Autoimmune neutropenia
Autologous haemopoietic stem cell transplantation
Coagulation factor inhibitors
Diamond Blackfan syndrome
Evans syndrome
Foeto-maternal/neonatal alloimmune thrombocytopenia
Haemolytic disease of the newborn
Haemolytic transfusion reaction
Haemophagocytic syndrome
Neonatal haemochromatosis
Paraprotein-associated demyelinating neuropathy
POEMS
Post-transfusion purpura
Primary immunodeficiencies, HSCT in
Pure red cell aplasia
Pure red cell aplasia
Pure white cell aplasia
Sickle cell disease
Systemic capillary leak syndrome

**Immunology**
Behçet's disease
Rheumatoid arthritis
Scleromyxedema
Sjogren's syndrome
Specific antibody deficiency (including IgG subclasses)
Systemic juvenile idiopathic arthritis
Systemic lupus erythematosus
Thymoma with immunodeficiency

**Infectious**
Chronic fatigue syndrome
Clostridium difficile colitis - severe or recurrent
HIV in children
Post-exposure prophylaxis for viral or pathogenic infection
Sepsis

**Multi-system**
Systemic lupus erythematosus
Transplantation (solid organ)

**Neurology**
Acute disseminated encephalomyelitis
Acute idiopathic dysautonomia
Acute optic neuritis
Adrenoleukodystrophy
Alzheimer's disease
Amyotrophic lateral sclerosis
Autism
Autoimmune encephalitis (including NMDA and VGKC)
Chronic facial pain
CNS vasculitis
Complex regional pain syndrome
Devic disease
Diabetic amyotrophy
Diabetic proximal neuropathy
Epilepsy
Hashimoto encephalopathy
Inflammatory myopathies
Lambert–Eaton myasthenic syndrome
Limbic encephalitis, nonparaneoplastic
Motor neuron disease/amyotrophic lateral sclerosis
Multifocal motor neuropathy
Multiple sclerosis
Myalgic encephalomyelitis
Myasthenia gravis
Narcolepsy/cataplexy
Neuromyotonia
Obsessive compulsive disorders
Opsoclonus myoclonus ataxia
Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections
PANDAS
Paraneoplastic syndromes
Polyneuropathy of critical illness
Potassium channel antibody-associated encephalopathy
Rasmussen syndrome
Stiff person syndrome
Susac syndrome

**Ophthalmology**
Autoimmune uveitis
Graves' ophthalmopathy

**Renal**
ANCA-positive systemic necrotising vasculitis
Glomerulonephritis — IgA nephritis
Haemolytic uraemic syndrome
Nephrotic syndrome

**Respiratory**
Asthma