

First National Immunoglobulin Database Report (2008–2009)

Editor
Professor Carrock Sewell

January 2010



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Executive summary

Data presented here are a unique, detailed view of current prescribing practice of immunoglobulin in England. Seven NHS Consultants, three Commissioners, and four database support staff created this report under the direction of Dr Denise O'Shaughnessy of the Blood Policy Unit, Department of Health, and Carrock Sewell, Visiting Professor of Immunology at the University of Lincoln, in the period October–December 2009. Although the findings presented are limited in scope in a number of ways, this report is important as it establishes, for the first time, a baseline of immunoglobulin use. This is a major step forward in establishing the Department of Health's Demand Management Programme and, in particular, validating the key step of prioritisation of treatment indications to ensure that immunoglobulin will always be available to those for whom the treatment is life-saving.

Background

"Variable supply, high product costs, and an increasing demand for both established and off-label indications have made the Department of Health's development of a management programme for intravenous immunoglobulin use in the United Kingdom essential."

The Department of Health's Demand Management Programme for Immunoglobulin was a key output from the 2006 review that assessed the opportunities available to secure the supply of immunoglobulin. The review recommended two complementary work streams, one based on securing supply and the other giving structure to the process of fulfilling demand (the Demand Management Programme), which necessitated the creation of the National Immunoglobulin Database (Reference number ROCR/OR/0221). The database was launched in June 2008 to record all immunoglobulin prescribing in England.

Data management

The Department of Health has focused on developing and enhancing the usability and functionality of the database in response to feedback from users, in particular with regard to ease of data entry and data management, and the development of reporting services. The database now resides on the NHS network, taking advantage of NHS infrastructure and technologies that support the enhanced functionality that has been

developed. In particular, the database operates a sophisticated information service that offers real-time online access to provider data for Commissioners and the Department of Health.

Data caveats

A number of important issues that influence data interpretation have become obvious during the preparation of this report and should be reviewed before the bulk of the report. These include incomplete infusion data, no disease recorded in some cases, and disease classified as 'other' when the treatment has been prescribed for an established indication, but the most important to highlight is the recording of inappropriate Panel-assigned prioritisation. The Demand Management Programme introduced colour coding to reflect the prioritisation of immunoglobulin treatment, based on availability of alternative treatments and strength of clinical evidence. There are many cases where diseases have been mis-assigned to an incorrect prioritisation. This distorts the data and compromises a key goal of this report, which is to identify accurately the distribution of immunoglobulin prescribing according to the prioritisation system. Looking to the future, there must be continued improvements to ensure the best possible data are available for accurate linking to payments by use. The Model Commissioning Policy states: 'Centres are expected, *without exception*, to provide a complete dataset to the Department of Health IVIG/SCIG Database in line with information requests from the team overseeing the IVIG/SCIG Database. This will be monitored and ongoing failure to provide data may lead to penalty payments.'

General findings

The data presented are for the 1-year period 18th September 2008 to 17th September 2009. The analyses are of 5119 patients for whom we know the diagnosis and include a total of 1,168,562 g of immunoglobulin. At the time of data extraction, 161 Trusts had enrolled in the database. Of the 168 acute Trusts in England, 12 had not registered for the database. There has been considerable effort from most Trusts to enter data, but some have entered little data and some Trusts have entered no infusion data. This is illustrated by comparing the ~2300 kg allocated by PASA to the ~1200 kg of infusions entered into the database. The cost of immunoglobulin is ~£35 per gramme; thus, treatment with immunoglobulin represents a substantial financial commitment for the health service, with an annual

purchase cost to the NHS in England of ~£80 million. Intravenous and subcutaneous immunoglobulin remains a high-cost drug exclusion from the national tariffs and is funded by PCTs, generally without restriction on use (i.e., budgets not capped).

Immunoglobulin use in specialisms

Neurology is the largest user (43% of volume), almost entirely due to two neuropathies (chronic inflammatory demyelinating polyradiculoneuropathy and multifocal motor neuropathy). Immunology is the second largest user (31%), almost entirely for primary immunodeficiency disorders, which are the highest overall user of any disease. Haematology and haemato-oncology together account for 17% of volume, with idiopathic/autoimmune thrombocytopenic purpura and chronic lymphocytic leukaemia the primary indications (the fourth and fifth highest using indications overall). The remaining specialisms of rheumatology, dermatology, infectious diseases and transplantation account for 9% of the volume used.

Immunoglobulin use according to colour-coded prioritisation

The infusion records show that 41% of the immunoglobulin used was prescribed under an assigned Panel decision of Red, 40% under a Blue decision (35% long-term use) and 19% under another Panel decision. For patient numbers, the proportions are 45%, 29% and 26%, respectively. Despite the confusion in colour coding, this gives the Department of Health some idea of the minimum amount of immunoglobulin required to cover essential treatment if there was ever another severe shortage.

Regarding Blue Panel decisions, the figures confirm that many patients could be given an alternative treatment in a severe immunoglobulin shortage situation. Over the past year, there has been little expansion in the therapeutic plasma exchange services in England. Plasma exchange is an alternative treatment to immunoglobulin in a number of indications and has been shown to have equal efficacy to immunoglobulin in the neurology indication with the heaviest use of immunoglobulin (chronic inflammatory demyelinating polyradiculoneuropathy) but is currently not regarded as a viable alternative partly because of the limited plasma exchange services. Enhancing plasma exchange services will fulfil an unmet need and may act as an important buffer in times of severe immunoglobulin shortage. At St George's Hospital, London, investment in the service in 2008 enabled the establishment of a 24-hour service, and resulted in an immediate 70% increase in referrals for plasma exchange. In the 18-month period from April 2008 to October 2009, 780 plasma exchange procedures were completed, 71% for neurology and 19% for haematology indications.

Prescribing in 'Grey' indications is of interest and amounted to more than 31,000 g. Interestingly, the top 10 diagnoses include two 'Grey' indications: secondary antibody deficiencies and antibody-mediated rejection following solid organ transplantation. Secondary antibody deficiencies are commonly related to immunosuppressive pharmacotherapy, as noted in the Clinical Guidelines, and the evidence base for efficacy is generally weak. The situation for antibody-mediated rejection

following solid organ transplantation is less clear cut, with use particularly in patients undergoing kidney transplant.

A considerable volume of immunoglobulin was used with no specific diagnosis (151,000 g or 13% of total recorded immunoglobulin use).

Commissioners' view

The Commissioners acknowledge that this first report from the National Immunoglobulin Database begins to form a picture of how immunoglobulin is being prescribed. The data clearly show that improvements are required before the database is sufficiently robust to be able to link to payments by use. Key issues include the need for all Trusts to register and enter data, and the need to enter data that reflect the Demand Management Programme, in particular addressing the issue of inappropriate use of the Red/Blue/Grey colour-coded prioritisation.

Specific findings

Immunology

For the most part, patients with primary immunodeficiency have been appropriately assigned a Panel decision of Red, and there is virtually no evidence of inappropriate use of immunoglobulin in immunology. The distribution of usage appears to reflect previous estimates of national usage; in most areas, there is good consensus regarding the allocation of priority groups, reflected in the mainly appropriate Panel decisions. Of note, the diagnostic categories within primary immunodeficiency disorders in the database are currently poorly defined and confusing, and it is therefore not possible to interrogate the database regarding use of immunoglobulin in individual primary immunodeficiency disorders.

Haematology

Immunoglobulin use in non-malignant haematology is driven by idiopathic/autoimmune thrombocytopenic purpura; use in other haematology indications accounted for a very small proportion of national use. There was minimal use in 'Grey' indications, although the Panel decisions assigned for 'Grey' indications are largely incorrect. Reflecting on future use of immunoglobulin to treat idiopathic/autoimmune thrombocytopenic purpura, important changes in the availability and perceived safety of alternatives might be expected to have an impact on immunoglobulin prescribing, with the withdrawal of anti-D in August 2009 and concern regarding the increasingly reported association between rituximab and progressive multifocal leukoencephalopathy.

Neurology

Most (85%) neurological use is for the four most common indications, three of which are supported by good evidence for effectiveness both in the short and long term, where applicable. Use in 'Grey' indications is minimal, and most is supported by Panel decisions or has been referred appropriately to PCTs for consideration of funding. The use of immunoglobulin for indications prioritised by the Demand Management Programme as Black is very low. There is no evidence that immunoglobulin is being used widely for proliferating indications unsupported

by an evidence base. Full entry of all immunoglobulin use in England has not been achieved and, using the epidemiology of Guillain-Barré syndrome, between 48% and 60% entry has been achieved, which correlates with the estimates presented. Overall, the data demonstrate appropriate and controlled use of immunoglobulin for a wide range of neurological conditions, most of which is evidence based. This reflects positively on the neurologists in the UK, who have signed up to the demand management process and continue to treat their patients on the best evidence available.

Unanswered questions

The Clinical Guidelines do not provide specific dosing recommendations, but note that the normal immunomodulatory dose of 2 g/kg is usually divided into five daily infusions of 0.4 g/kg, although some physicians prefer to use two daily doses of 1 g/kg each. There is considerable interest in the potential benefits of such shorter dosing schedules and this is an area of research interest. At the moment, the database infusion records are incomplete and therefore it is difficult to fully interpret the data and it is not possible to decipher the dosing that has been used. Generally, the infusion data should be interpreted with caution. Data on neurology indications seem to be the most robust in the database, and the dosing data seem reasonable; for example, the average dose in patients with Guillain-Barré syndrome is 144 g, corresponding to just over 2 g/kg in a 70-kg average person.

There is considerable interest in the use of lean body weight-adjusted dosing of immunoglobulin. A pilot project in Australia has used reduced doses in obese patients, 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 Institute of Neurology in London has used a formula based on gentamicin dosing in the obese for 3 years. 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.

Where the database has not been successful is the capture of data regarding efficacy of immunoglobulin. Panels were encouraged to request up to three parameters by which efficacy could be determined in each patient (e.g., platelet count in patients with ITP). The purpose of this exercise was both to obtain preliminary data about efficacy in various conditions (fully accepting that lack of diagnostic criteria and other issues would make this a very crude analysis) and to provide feedback to individual Panels about the quality of their decision making. If Panels repeatedly approve indications prioritised as Grey by the Demand Management Programme and the treatment is largely ineffective, this statistic should improve Panel decision making. Given that we now know that most prescribing

has been for approved conditions, a more pragmatic approach may be to abandon efficacy tracking for conditions prioritised by the Demand Management Programme as Red or Blue. Commissioners will want to know that Panels are making effective decisions, so retaining efficacy tracking for 'Grey' indications only is a logical development for the future. To facilitate this, consideration should be given to predefined efficacy monitoring parameters for selected conditions, accepting that this is not possible for the entire gamut of human disease.

A vital aspect of the recording of individual infusions is the ability of the database to track product batches. The clinical community welcomed the introduction of the National Immunoglobulin Database because it would finally address this issue of batch tracking at a national level, and it was an important driver in promoting acceptance of the Demand Management Programme. However, difficulty in entering individual batch numbers has been considerable. Plans are under way to develop bar coding of individual products, but the wide variety of barcode formats used internationally makes this very difficult, as would the expense of equipping all relevant units with barcode readers and software. A third approach has been studied in Oxford recently, using pharmacy-produced bar codes for individual boxes of products that incorporate additional safety information (e.g., expiry date). On reflection, since all hospitals are already familiar with the processes involved in batch tracking of blood products, using similar processes (whether barcode- or paper-based) may facilitate more complete data entry in future and will be given serious consideration in updates of the database.

Unity of effort

The overall number of patients entered in the database as this report goes to press has reached about 10,000. *This represents a significant effort on behalf of most acute Trusts, and clinicians, pharmacists and others should be congratulated on this achievement.* Although many Trusts have made sterling efforts to enter complete data, it is apparent that this has not been possible in most cases; many cite lack of resources. Both Commissioners and clinicians are very keen that the process continues, but urgent consideration needs to be given to facilitating Trusts in entering complete data in a timely fashion. The linking of reimbursement for immunoglobulin expenditure to database entry, as proposed by the Commissioners, needs to be balanced with a 'carrot'. An example that has been used to good effect by the Yorkshire and Humber Specialised Commissioning Group in 2009/10 was including data completion as a goal within local CQUIN schemes, making a small proportion of provider income (0.5% of contract value in 2009/10) conditional on achievement of this locally agreed quality improvement and innovation goal.

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Abbreviations

ALL	acute lymphoblastic leukaemia
ANCA	anti-neutrophil cytoplasmic antibody
BMT	bone marrow transplantation
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CLL	chronic lymphocytic leukaemia
CVID	common variable immunodeficiency disorder
DH	Department of Health
GBS	Guillain-Barré syndrome
HPA	Health Protection Agency
HSCT	haematopoietic stem cell transplantation
ITP	idiopathic thrombocytopenic purpura
MDSAS	Medical Data Solutions and Services
MG	myasthenia gravis
MM	multiple myeloma
MMN	multifocal motor neuropathy
MMNCB	multifocal motor neuropathy with conduction block
MUD	matched unrelated donor
NSCG	National Specialised Commissioning Group
Panel	Immunoglobulin Assessment Panel
PCT	Primary Care Trust
PID	primary immunodeficiency disorder
RCT	randomised controlled trial
SCG	Specialised Commissioning Group
SHA	Strategic Health Authority
SLE	systemic lupus erythematosus

Terminology of the Demand Management Programme for Immunoglobulin

The Demand Management Programme for Immunoglobulin (which covers both intravenous and subcutaneous administration of normal human immunoglobulin) introduced colour-coded prioritisation of immunoglobulin prescribing in June 2008. It is essential that prescribers understand the definitions used; the prioritisation was designed to protect supplies of immunoglobulin for those most at need in times of shortage. Prescribing according to this prioritisation is defined in the prescribing approval process (Figure). The assumption was that accurate prescribing according to these definitions would allow simple tracking of prescribing patterns in the database and future developments are expected to include the linking of payment to Trusts for immunoglobulin treatment according to database entry.

Red indicates conditions for which treatment is considered the highest priority because of a risk to life without treatment, such as selected primary immunodeficiencies, Kawasaki disease and GBS. Clinicians may prescribe without prior approval, with retrospective completion of the immunoglobulin request form for sign-off by a designated person and subsequent database registration.

Blue indicates conditions for which, although the evidence base is reasonable, the treatment priority is moderate because other treatments are available. The local panel can approve use, but treatment should be considered on a case-by-case basis, prioritised against other competing demands for immunoglobulin, especially in times of shortage.

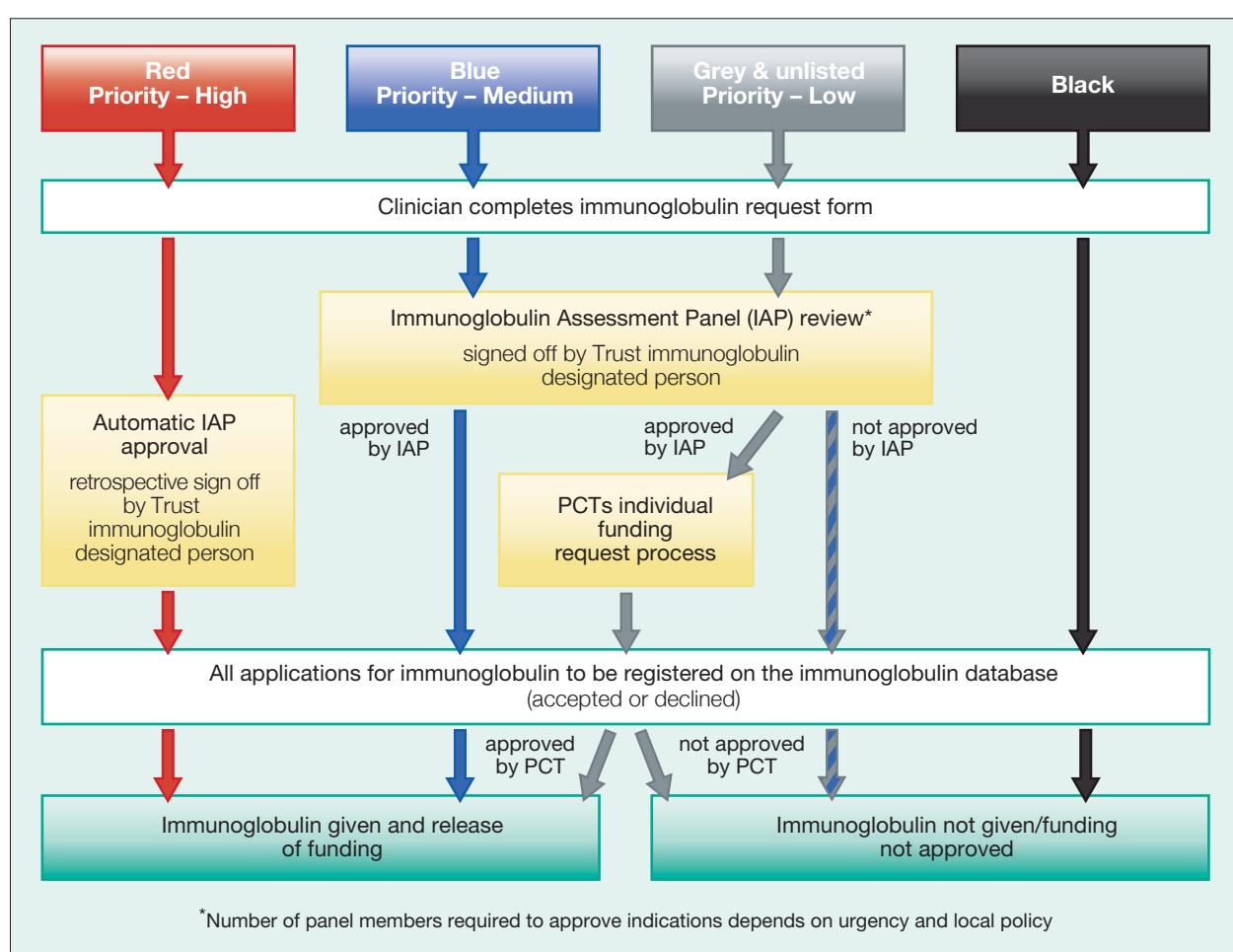


Figure Immunoglobulin prescribing approval process.

Grey indicates conditions for which the evidence base for immunoglobulin efficacy is weak, in many cases because the disease is rare. All diseases not specifically listed in the *Clinical Guidelines for Immunoglobulin Use* should be treated as Grey. For 'Grey' indications, approval from both the Panel and the PCT is required for immunoglobulin treatment. Again, treatment should be considered on a case-by-case basis, prioritised against other competing demands for immunoglobulin, especially in times of shortage.

Some 'Grey' conditions require very urgent treatment, in which case a pragmatic approach is needed: an emergency decision should be made at the time and negotiations with the PCT be carried out retrospectively.

Black indicates conditions for which there is evidence that immunoglobulin is not an appropriate treatment and treatment is not recommended. For 'Black' conditions, immunoglobulin treatment is automatically declined. However, 'exceptionality' can be applied and a form must be completed for Panel consideration.

The appropriateness of immunoglobulin treatment is denoted as yes (appropriate in all cases if the physician wants to prescribe it), selected (appropriate in only selected cases, if the physician wants to prescribe it) and no (not appropriate) (Table).

For all conditions, the intended duration of treatment should be recorded in the database (either short or long term). Short-term treatment is defined as treatment in serious or potentially life-threatening conditions and/or consisting of a single course of treatment, which may comprise up to three doses. A single dose is defined as the appropriate dosage for the disease indication (usually in g/kg), which may be fractionated and delivered over 1–5 days. Long-term treatment is defined as one or more courses of immunoglobulin where further courses may be anticipated from the diagnosis before the initiation of treatment or decided upon following response to a single trial course.

For treatment requests that fall outside these definitions, a funding request sanctioned by the local Panel can be made to the local Commissioner for consideration before treatment under exceptionality.

Table Summary of recommendations for immunoglobulin therapy in diseases for which the treatment prioritisation is high (Red) or moderate (Blue)

Condition	Treatment		Recommendation, evidence grade*
	Short term	Long term	
Immunology			
Impaired specific antibody production	No	Selected	C, III
Kawasaki disease	Yes	No	A, Ia
Primary immunodeficiencies	selected	Yes	B, IIb
Haematology			
Acquired red cell aplasia caused by parvovirus B19	Selected	No	C, III
Adult HIV-associated thrombocytopenia	Selected	No	A, Ib
Alloimmune thrombocytopenia – fetal therapy (treatment to the mother)	Yes	No	C, III
Alloimmune thrombocytopenia – neonatal therapy	Selected	No	C, III
Autoimmune (acquired) haemophilia	Selected	No	C, III
Autoimmune haemolytic anaemia	Selected	No	C, III
Autoimmune thrombocytopenia (see ITP)	Selected	No	A, Ia
Evans' syndrome	Selected	No	C, III
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	Selected	No	C, III
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome	Selected	No	C, III
Idiopathic thrombocytopenic purpura – paediatric (<16 years)	Selected	No	A, Ib
Idiopathic thrombocytopenic purpura – adult	Selected	No	A, Ia
Post transfusion purpura	Selected	No	C, III

continued ►►►

***Grade A:** Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency evaluating the specific recommendation (evidence levels Ia, Ib). **Grade B:** Requires the availability of well conducted clinical studies but not randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb). **Grade C:** Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities; indicates an absence of directly applicable clinical studies of good quality (evidence levels III, IV)

Condition	Treatment		Recommendation, evidence grade*
	Short term	Long term	
Haemato-oncology			
Chronic lymphocytic leukaemia	No	Selected	A, Ib
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome	Selected	No	C, III
Low serum IgG levels after haematopoietic stem cell transplant for malignancy	Yes	Selected	B, IIb
Multiple myeloma	No	Selected	A, Ib
Neurology			
Chronic inflammatory demyelinating polyradiculoneuropathy	Selected	Selected	A, Ia
Dermatomyositis	Selected	Selected	B, IIa
Guillain-Barré syndrome	Selected	No	A, Ia
Lambert Eaton myasthenic syndrome	Selected	Selected	A, Ib
Multifocal motor neuropathy	Selected	Selected	A, Ia
Myasthenia gravis	Selected	Selected	B, Ia
Paraprotein-associated demyelinating neuropathy (IgG or IgA)	Selected	Selected	A, Ia
Paraprotein-associated demyelinating neuropathy (IgM)	No	Selected	A, Ib
Rasmussen syndrome	No	Selected	B, IIb
Stiff person syndrome	No	Selected	A, Ib
Dermatology			
Dermatomyositis	Selected	Selected	B, IIa
Immunobullous diseases	Selected	Selected	C, III
Toxic epidermal necrolysis, Steven's Johnson syndrome	Yes	Selected	B, IIa
Paediatrics			
Alloimmune thrombocytopenia – neonatal therapy	Selected	No	C, III
Fetal hydrops	Selected	No	D, IV
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	Selected	No	C, III
Idiopathic thrombocytopenic purpura (< 16 years)	Selected	No	A, Ia
Toxin-related infection in paediatric intensive care	Selected	No	C, III
Paediatric rheumatology			
Juvenile dermatomyositis	Selected	Selected	B, IIa
Kawasaki disease	Yes	No	A, Ia
Adult rheumatology			
Dermatomyositis	Selected	Selected	B, IIa
Infectious diseases			
Necrotising (associated with Panton Valentine leukocidin) staphylococcal sepsis	Selected	No	C, III
Severe invasive group A streptococcal disease	Selected	No	B, Ib
Severe or recurrent <i>Clostridium difficile</i> colitis	Selected	No	C, III
Staphylococcal toxic shock syndrome	Selected	No	C, III
Transplantation			
Pneumonitis induced by cytomegalovirus following transplantation	Yes	No	A, Ib

Data management and caveats

The new database operates a sophisticated information service that offers real-time online access to provider data for Commissioners and the DH. This service provides flexible reporting with filters and export options to customise data access and was used to extract and analyse the data presented in this report. The real-time nature of the data means that data extractions represent the data available at that moment in time. A consequence is that the data presented in the report are not reproducible as the data are dynamic.

The data presented were extracted for a 1-year period (18th September, 2008 – 17th September, 2009) over several days in early October 2009, with the exception of Chapter 3; the analysis of immunoglobulin prescribing in The East of England was conducted on data extracted on 17th November, 2009. A new database was commissioned during this 1-year period and implemented on 1st June, 2009.

As expected, this first detailed review of the data has identified a number of issues with completeness of data entry, quality and management, in particular in relation to how the Panel decisions about colour-coded prioritisation are recorded. In most cases, these issues were due to information not being available to the pharmacist at the point of entry to the database. A number of important issues that influence data interpretation are noted below and should be reviewed before the bulk of the report.

Immunoglobulin infusion data recorded are incomplete: The database asks users to enter detailed records of individual infusions. This is an onerous task for some Trusts and data entry is variable, especially for patients who are receiving home delivery, for whom this information can be difficult to obtain. Some Trusts enter meticulous records of infusions in real time, others group the infusion data entry to a single time (e.g., monthly) and some Trusts have completed no infusion data. Therefore, the volumes presented are incomplete and all dose data and average dose estimates should be interpreted with caution.

Disease diagnosis is not recorded: Around 15% of Panel decisions entered into the database have no patient diagnosis recorded. Although the corresponding volume of immunoglobulin was included in the volume analysis of immunoglobulin use per Trust, these cases could not be included in disease-specific analyses without a diagnosis.

Disease diagnosis recorded as ‘other’: Many patients receive immunoglobulin with a specified diagnosis of ‘other’. The option of ‘other’ was offered in the database specifically to allow the entry of rare indications or clinical scenarios that are not listed in the Clinical Guidelines. However, a substantial proportion of these cases record the disease as ‘other’ despite the option to select the disease from the guideline-specific disease listing.

Inappropriate Panel-assigned prioritisation:

The Demand Management Programme introduced colour coding to reflect the prioritisation of immunoglobulin treatment, based on availability of alternative treatments and strength of clinical evidence (see pages x–xii). There are many cases where diseases have been mis-assigned to an incorrect prioritisation. For example, patients with primary immunodeficiencies should always be assigned a Red decision by the local Panel. Even if a disease is life-threatening and immunoglobulin is used as a last resort in an indication prioritised as Grey by the Demand Management Programme, this should be assigned the correct Panel decision of Grey and not Red, as has been the case in many Panel decisions. Functionality is being considered in the new database to tighten up on this problem.

Panel decision is not recorded: Among the data imported from the old database, 179 Panel episodes have no Panel decision recorded. These entries have been included in the analyses. In addition, a large number of cases are recorded in the database as ‘awaiting Panel decision’. This caused concern and suggested that the Panels were not operating as expected and not making timely decisions on prescribing. However, in a substantial proportion of these cases (not fully determined how many), this reflects a problem with data entry into the old database, when data entry was not saved correctly, and this became apparent only after the new database system was launched.

Orphan infusions: Among the data imported from the old database, 29 infusion records are not linked to a Panel decision, patient or diagnosis. These infusions have been excluded from all analyses.

Multiple diagnoses: 324 patients have more than one diagnosis listed. These patients and the volumes used are included for each diagnosis listed.

Panel episodes and patient numbers: The data presented on alternative treatments tried and plasma exchange are by Panel episode (i.e., each time a Panel decision is recorded) and do not represent patient numbers. This is because the database does not link alternative treatments directly to a diagnosis. Thus, a patient with multiple diagnoses and multiple Panel decisions will appear a number of times.

Lack of GP practice code: Only around one-third of patients have been linked to their GP practice code, which makes it impossible to carry out any accurate analyses of use per PCT or SHA. In the new database, functionality has been provided to improve completeness in this area.

Introduction

Denise O'Shaughnessy

1.1 Department of Health Demand Management Programme for Immunoglobulin

"Variable supply, high product costs, and an increasing demand for both established and off-label indications have made the Department of Health's development of a management programme for intravenous immunoglobulin use in the United Kingdom essential."

Fitzharris P, Hurst M. *BMJ* 2008; 337:a1851

The commentary quoted above from the *BMJ* succinctly presents the need for the DH's Demand Management Programme and sets the scene for this first report from the National Immunoglobulin Database. The National Immunoglobulin Database was created as part of a larger national Demand Management Programme for Immunoglobulin, sponsored by the DH. This includes a *Demand Management Plan for Immunoglobulin Use*, which recommends that Trusts or Strategic Health Authorities (SHAs) establish a local Panel to approve and monitor the local prescribing of immunoglobulin, and the *Clinical Guidelines for Immunoglobulin Use*. The guidelines were published in 2007, with the second edition published in 2008 after stakeholder review. Although formulated for use in England, the guidelines have now been adopted in Scotland. The Demand Management Programme can be accessed at www.ivig.nhs.uk.

The key process across all three components of the Demand Management Programme has been the introduction of prioritisation of treatment indications. Immunoglobulin remains the only treatment option for primary immunodeficiencies and, in certain other diseases, immunoglobulin is life saving. Shortages must never jeopardise supply for these patients and this factor was given primary consideration in the formulation of the Demand Management Programme. To ensure the availability of immunoglobulin in times of shortage, colour coding of treatment indications according to prioritisation (see Table, pages xi-xii) defines the prescribing approval process (see Figure, page x) and allows simple tracking of prescribing patterns in the database, if applied appropriately.

Demand Management Programme timeline

On 30th May 2008, the DH published revised versions of the *Clinical Guidelines for Immunoglobulin Use* and *Demand Management Plan for Immunoglobulin Use* (Gateway reference 10012 and 10013). The DH issued a 'Dear Colleague' letter (DH_085234) on 3rd June highlighting the release of these documents and the importance of the programme to maintain the security of supply of immunoglobulin. The National Immunoglobulin Database (Reference No. ROCR/OR/0221) was launched on 2nd June 2008, with NHS MDSAS contracted at launch to continue the database programme and to be responsible for working with a DH-sponsored database steering group to maintain and extend the solution. See www.ivig.nhs.uk to access these documents.

1.2 History of the National Immunoglobulin Database

In 2006, precipitated by the immunoglobulin supply shortage, the DH initiated a review to assess the opportunities available to secure the supply of immunoglobulin in England and to develop a more evidence-based approach to immunoglobulin use. At the beginning of the review, the DH sponsored a survey of English pharmacists to understand immunoglobulin prescribing patterns. The findings of the survey showed that the neurology specialism accounted for the largest proportion of immunoglobulin use (39%), around double the use in haematology (20%) and more than double the use for immunology (16%) (Figure 1.2). Around one-quarter of immunoglobulin prescribing was designated as 'other'. At this point, the size of the market was 2300 kg at a total cost of approximately £54 million. These findings were helpful; the review recommended two complementary work streams, one based on securing supply and one giving structure to the process of fulfilling demand, which were agreed by the DH and initiated in late 2006. A key recommendation in the review to support both work streams was the

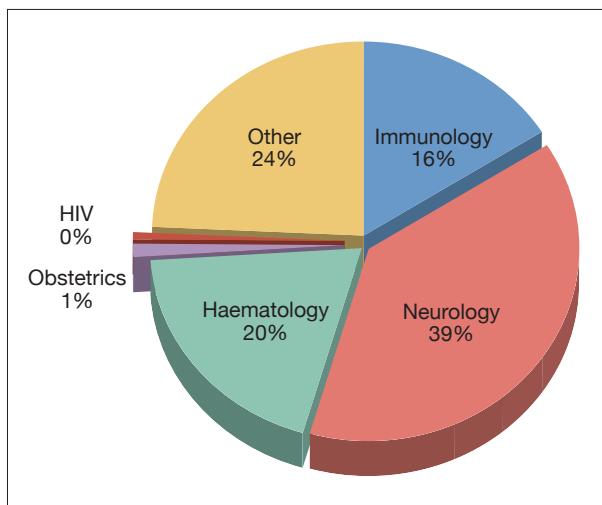


Figure 1.2 Survey of immunoglobulin use in England in 2006 across pre-specified clinical specialisms.

creation of a national database to record prescribing. The database was launched in June 2008.

1.3 Technical aspects and development of the National Immunoglobulin Database

The first iteration of the database went live in June 2008. The plan following launch was to develop and enhance functionality in response to feedback from users and service developments. Soon after the database was launched, users reported that the system was slow and sometimes unstable, and data entry was time consuming. In response, DH initiated major revisions to improve functionality and ease of use and the database was moved in-house to take advantage of NHS infrastructure and technologies.

The database is now built around the very latest technologies, utilising Microsoft Products as used by the NHS IT Connecting for Health programme. These include SQL Server (2008 version), Reporting Services and ASP.NET (3.5 version). These technologies, together with use of the internal NHS network, enabled all the key re-development objectives to be met.

Two integrated systems were developed to best meet the needs of all stakeholders (Trusts, Commissioners and DH) (Figure 1.3). The database allows Trusts to enter and review their immunoglobulin use. The Information Service allows real-time online access to provider

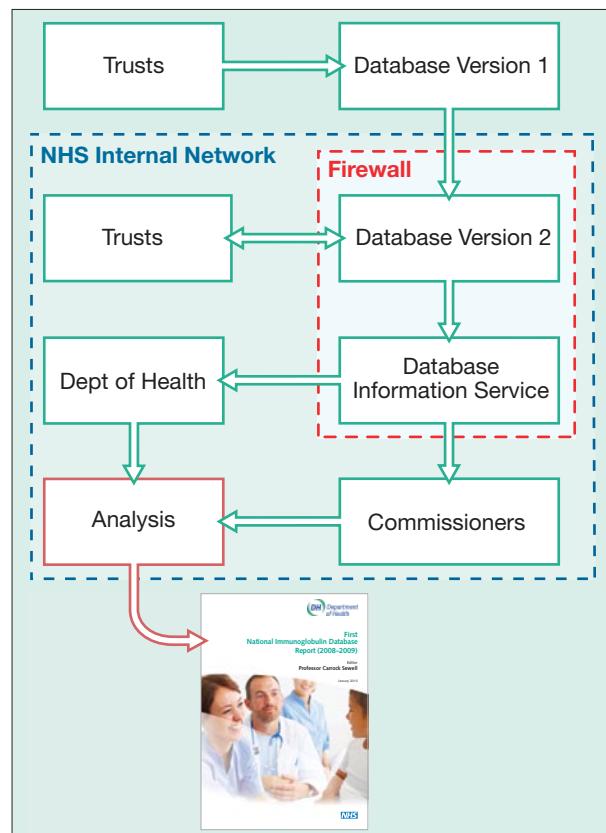


Figure 1.3 Immunoglobulin database system structure.

data for Commissioners and DH. This service also provides flexible reporting with filters and export options to customise data access (see Chapter 3) and was utilised to prepare this report.

1.4 Aims of the National Immunoglobulin Database

The database records immunoglobulin prescribing in England. The initial aims of the database were to allow more accurate assessment of immunoglobulin use for forecasting and tendering, and also to provide an accurate picture of prescribing by indication and a tracking mechanism of individual batches of immunoglobulin for safety purposes. These aims have developed further; with the publication of the Model Commissioning Policy by the NSCG, there is now an explicit desire to link immunoglobulin use to payment at the PCT or SHA level through the records contained in the database.

The database has been operational for 18 months. This report sets out the first analysis of the database and provides an assessment of how the dataset is functioning with regard to these aims. There have been a number of issues with regard to its smooth operation, such as speed and complexity of data entry, but MDSAS, partly through its new system developed in-house, have taken the lead

on the database programme and have been working closely with the DH-sponsored database steering group to enhance the database and ensure its smooth running. This report will be considered by the database steering group and decisions will be taken in early 2010 on improvements to database functionality to ensure the database can provide the outputs required to fulfil its role.

Overview of immunoglobulin use

Denise O'Shaughnessy and Carrock Sewell

Although immunoglobulin preparations were first used therapeutically in the 1950s as immunoglobulin replacement therapy for primary immunodeficiency disorders, it was not until technological advances in the fractionation of plasma about 30 years ago that monomeric solutions of IgG suitable for intravenous use were developed. The seminal discovery of the immunomodulatory activity of intravenous immunoglobulin in childhood ITP opened the door to a rapid expansion of use in autoimmune diseases, particularly in haematology and neurology, and prescribing has continued to expand and crossed over into almost every medical specialty. The DH-sponsored survey in 2006 (see page 1) offered initial insights into immunoglobulin prescribing, but this chapter sets out, for the first time, a detailed assessment of immunoglobulin prescribing in England, with the provisos attached to the data as described on pages xiii–xiv.

2.1 Entries in the database

The data presented in this Annual Report are for the 1-year period 18th September 2008 to 17th September 2009. The analyses are of 5119 patients for whom we know their disease diagnosis (patient exclusions are described on pages xiii–xiv) and include a total of 1,168,562 g of immunoglobulin (volumes described in this report represent the infusions that have been recorded in the database, which are incomplete). The data in the database are ‘live’, and data are changing in real time as details are back-filled (e.g., on 02/12/2009, infusion volume recorded for the same 1-year period had increased 11% to 1,302,187 g). As further data are entered for patients treated in this period, the data will become more accurate. Therefore, it is important to enter all patient data, even if the treatment dates are long past.

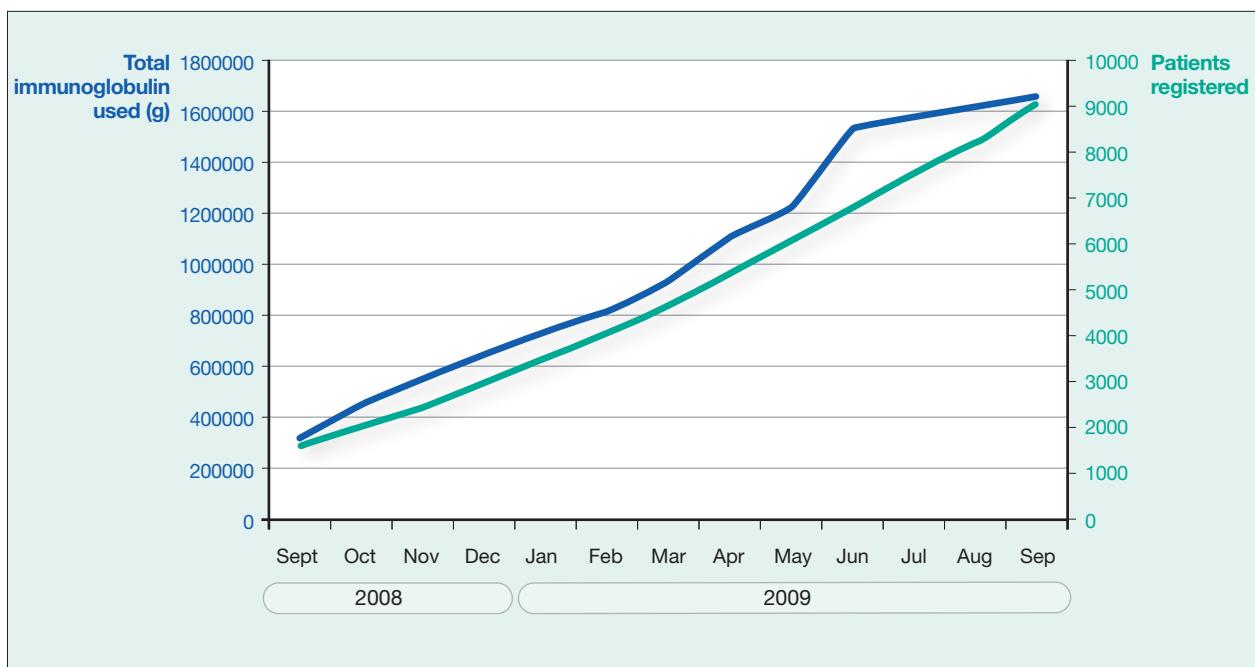


Figure 2.1 Growth of the database in terms of patients registered and volume of immunoglobulin use recorded.

At the time of data extraction, 161 Trusts had enrolled in the database. Of the 168 acute Trusts in England, 12 had not registered for the database. Not all NHS Trusts are expected to enrol, as some will never use immunoglobulin therapy (e.g., mental health and ambulance Trusts). However, some specialist Trusts that would be expected to use immunoglobulin had not registered. There has been considerable effort from most Trusts to enter data, but some Trusts have entered very little data. This is illustrated by comparing the ~2300 kg allocated by PASA to the ~1200 kg of infusions entered into the database. This suggests that about half of all immunoglobulin use has been entered.

Since the database was launched in June 2008, it has grown steadily both in the numbers of patients registered and the volume of immunoglobulin use recorded. The data growth for the period of this analysis is shown in Figure 2.1.

2.2 Immunoglobulin use in specialisms

As expected from the 2006 survey, neurological conditions account for more immunoglobulin use than any other specialism. However, the relative values may not be truly representative because data records are more complete for neurology than for any other specialism.

2.3 Immunoglobulin use in individual NHS Trusts

The number of patients entered by each Trust and the volume of infusions varies considerably (0–433 patients and 0–102,000 g). Clearly some Trusts will treat patients with immunoglobulin rarely, and others, for example those that incorporate tertiary referral centres, are significant users of immunoglobulin therapy, but some Trusts have not entered patient data, as noted above. Regarding infusion volumes, Trusts have been variable in their data entry, and for some Trusts, no information is available on the volume infused.

The largest number of patients was entered at Imperial College Healthcare NHS Trust. The majority of immunoglobulin use at Imperial is in transplantation and neurology patients (Figure 2.3.2). The largest volume user, with the highest average volume recorded per patient (~400 g) is University College London Hospitals NHS Foundation Trust. This Trust includes the National Hospital for Neurology and Neurosurgery, which as expected is a high volume user of immunoglobulin; neurology indications dominate the breakdown of this Trust's immunoglobulin use, as shown in Figure 2.3.3.

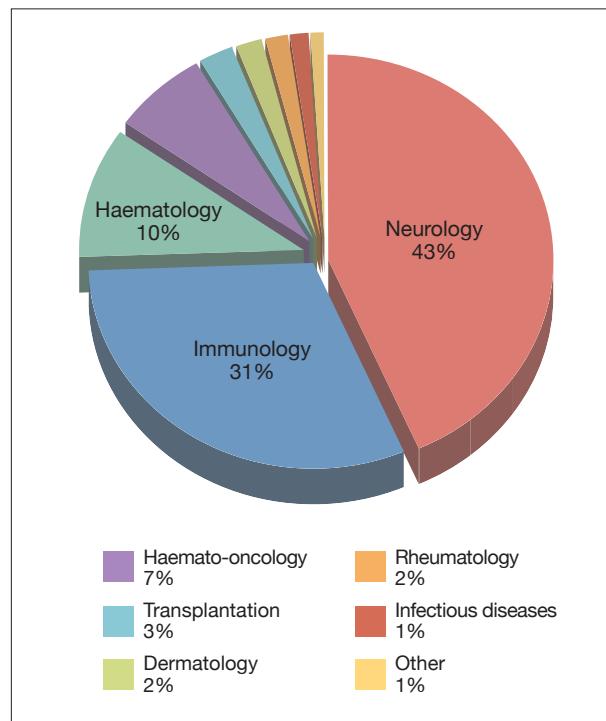


Figure 2.2 Volume of immunoglobulin used for each specialism. The infusion data recorded in the database are incomplete; these data should be interpreted with caution.

Table 2.3.1 Number of patients and volume of immunoglobulin used in top 10 Trusts

NHS Trust	N	G
Imperial College Healthcare NHS Trust	433	42,322
Oxford Radcliffe Hospitals NHS Trust	321	63,722
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	318	92,261
Barts And The London NHS Trust	295	13,906
University College London Hospitals NHS Foundation Trust	266	102,840
Leeds Teaching Hospitals NHS Trust	261	68,195
Salford Royal NHS Foundation Trust	256	62,479
Royal Free Hampstead NHS Trust	244	63,705
Great Ormond Street Hospital For Children NHS Trust	185	8122
Southampton University Hospitals NHS Trust	171	(27,639)*
Total	2750	517,552

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. *Data provided by the Trust as this report was going to press; volume not included in the database or in the total.

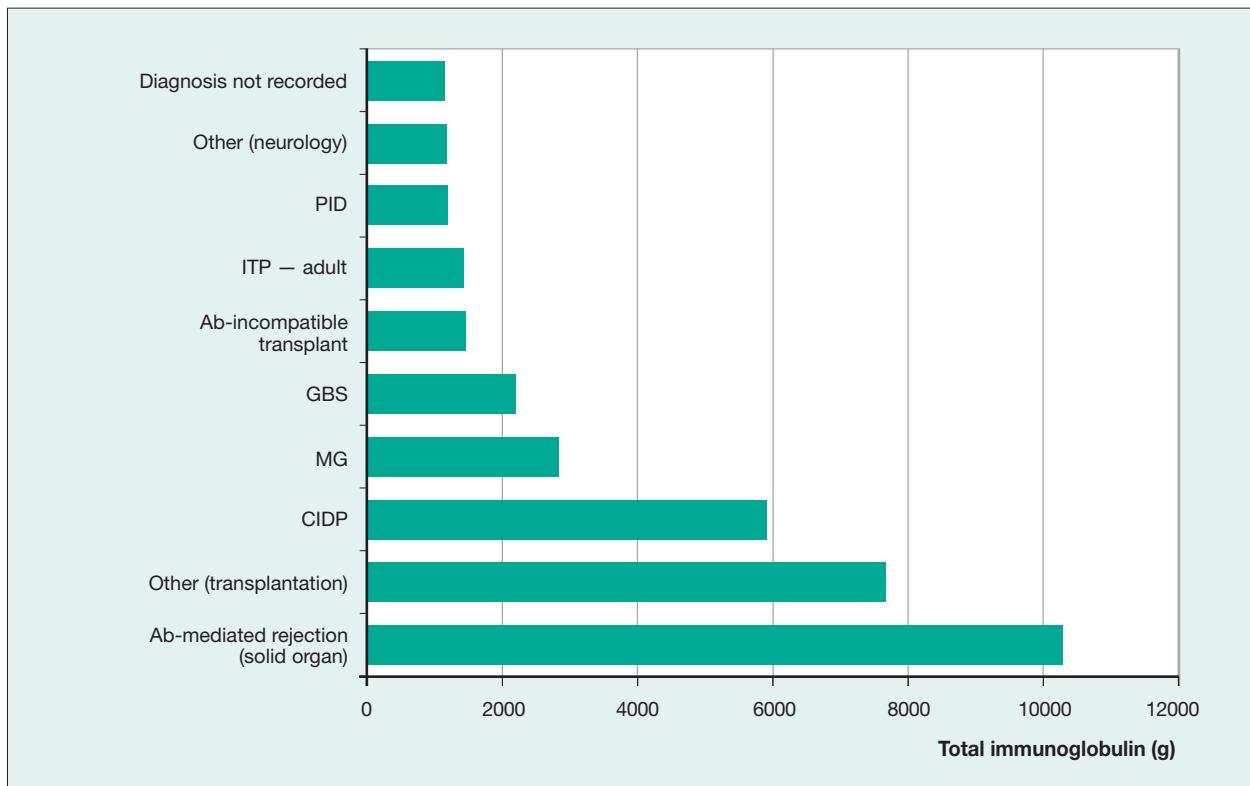


Figure 2.3.2 Immunoglobulin use at Imperial College Healthcare NHS Trust.

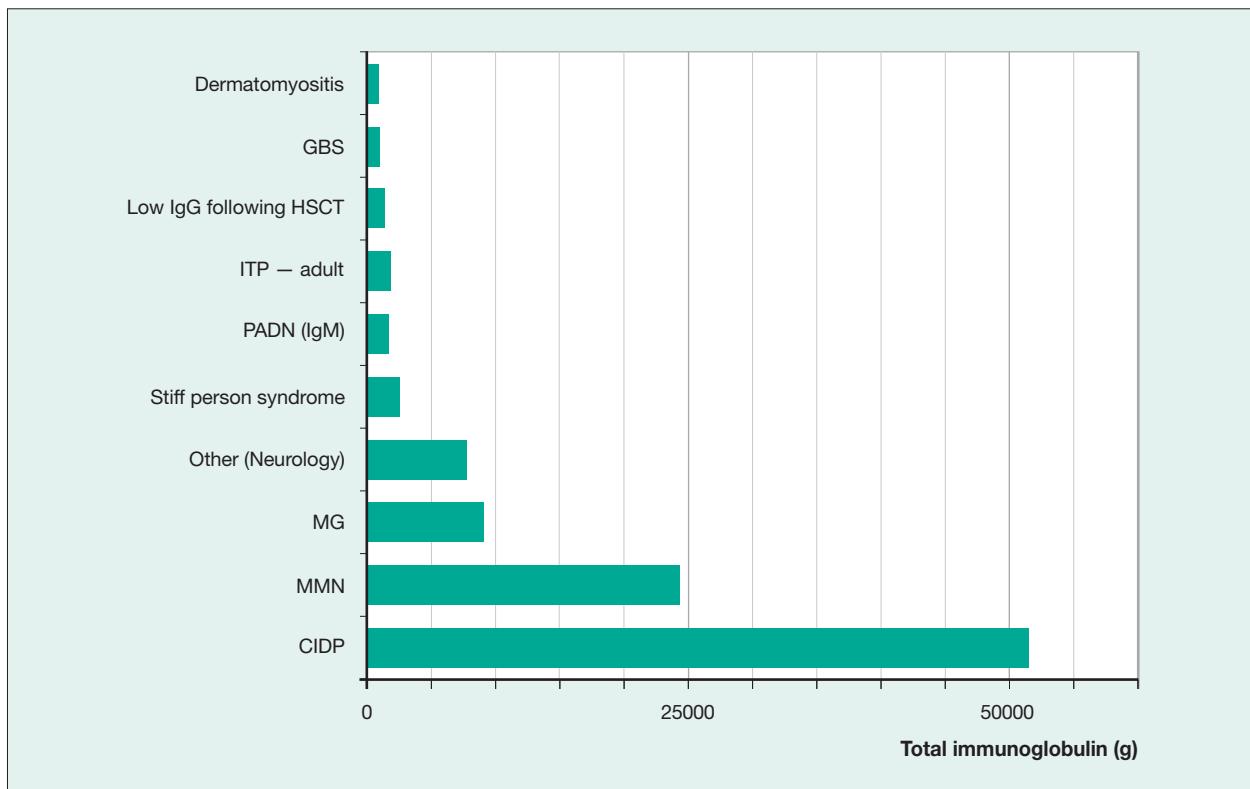


Figure 2.3.3 Immunoglobulin use at University College London Hospitals NHS Foundation Trust.

2.4 Immunoglobulin use for top 10 individual diagnoses

At the initiation of the Demand Management Programme, there was a concern that large amounts of immunoglobulin were being used to treat conditions for which there is little evidence of efficacy. This does not appear to be the case from the data presented.

As might be expected, PIDs account for the largest number of patients receiving immunoglobulin therapy (1246) and the greatest volume used (295,837 g or 25% of all recorded use). The PIDs are prioritised as Red by the DH Demand Management Programme (see Terminology of the Demand Management Programme for Immunoglobulin, page x). The next greatest volume used is for CIDP (231,694 g or 20% of all recorded use). The top 10 diagnoses (by volume) include four neurology indications; there are four 'Red', four 'Blue' and two 'Grey' indications. Prescribing in 'Grey' indications is of interest and amounted to more than 31,000 g. Secondary antibody deficiencies are commonly related to

immunosuppressive pharmacotherapy as noted in the guidelines and the evidence base for efficacy is generally weak. The situation for antibody-mediated rejection following solid organ transplantation is less clear cut, with use particularly in patients undergoing kidney transplant. The Grey designation of this indication is reviewed again in Chapter 13.

2.4.1 Immunoglobulin use for 'other' diagnoses

A considerable volume of immunoglobulin was used with no specific diagnosis (151,000 g or 13% of total recorded immunoglobulin use). For some patients treated under a diagnosis of 'other', additional details were available in the patient record (see later chapters). To ensure that this important information can be accessed and tracked accurately in the database in the future, the primary diagnosis for which the patient is receiving immunoglobulin should be selected, even if the diagnosis is not confirmed at the time of the request; this can be revised later if necessary.

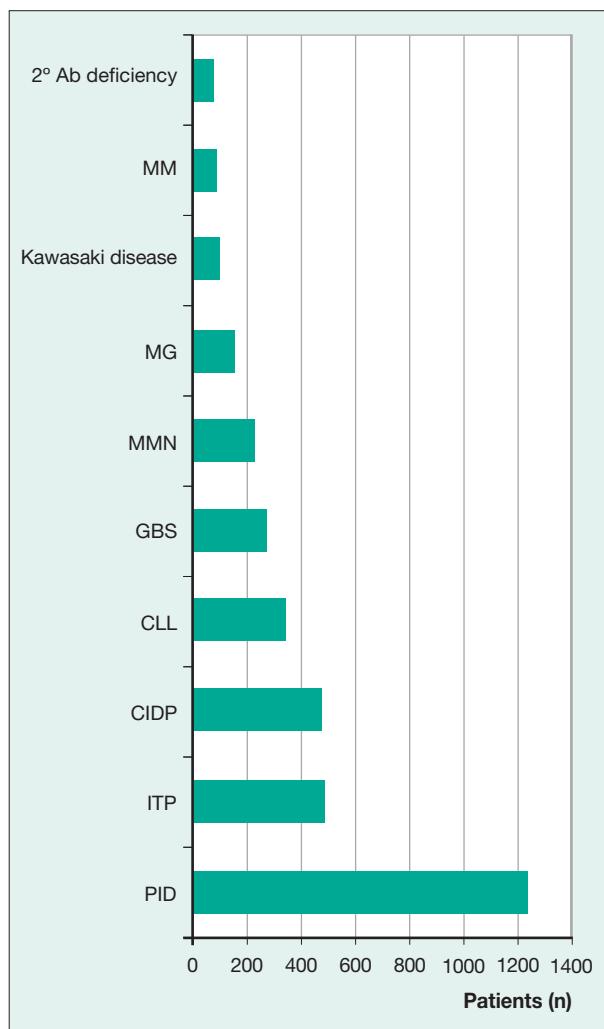


Figure 2.4.1 Number of patients receiving immunoglobulin for top 10 individual diagnoses.

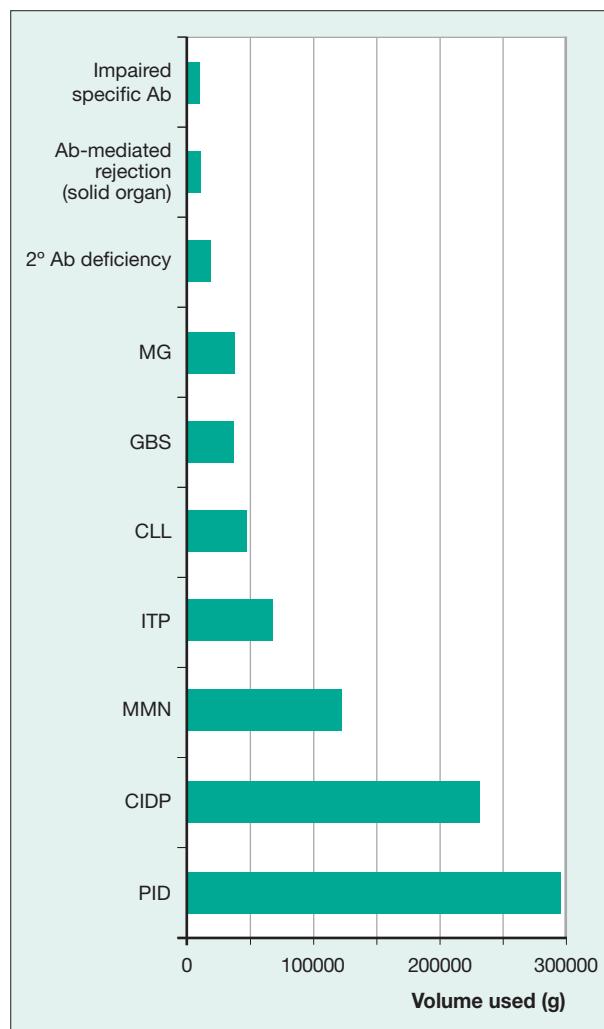


Figure 2.4.2 Volume of immunoglobulin (from recorded infusion data) used for top 10 individual diagnoses. The infusion data recorded in the database are incomplete; these data should be interpreted with caution.

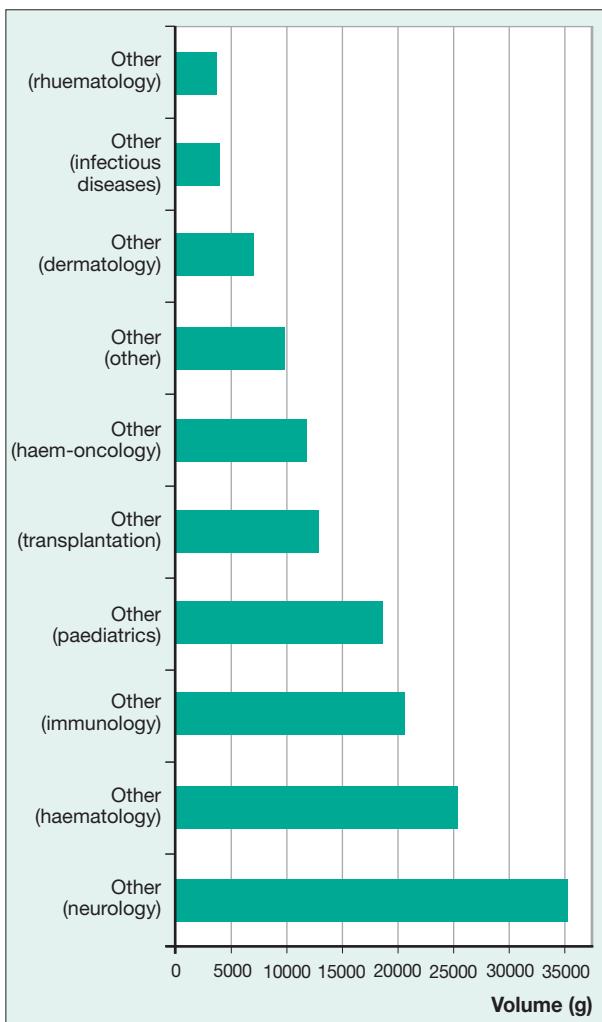


Figure 2.4.3 Volume of immunoglobulin used where no specific diagnosis was recorded. The infusion data recorded in the database are incomplete; these data should be interpreted with caution.

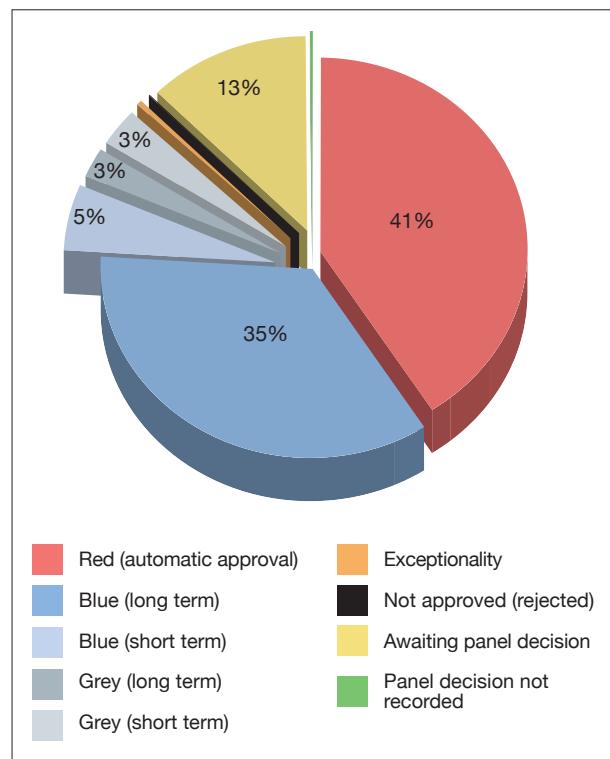


Figure 2.5.1 Volume of immunoglobulin used by assigned Panel decision. The infusion data recorded in the database are incomplete; these data should be interpreted with caution.

these ‘Grey’ indications should be recorded as Grey in the database, even if their approval is similar to Blue.

2.5.1 Immunoglobulin use according to assigned Panel decision

The 10 diagnoses that account for the greatest volume of immunoglobulin use illustrate this variation. Table 2.5 and Figure 2.5.2 show the numbers of patients with each diagnosis and the assigned Panel decision; the prioritisation in the Demand Management Programme is shown in the Table by shading.

The top five diagnoses by volume of immunoglobulin use are PID, ITP, CIDP, CLL and GBS. Most prescribing for these appears appropriate, although there are some inappropriate Panel decisions. It is not possible in the current system to distinguish short- and long-term treatment where the Panel decision is Red. Therefore, it is not clear whether all patients assigned a Panel decision of Red were treated for the appropriate duration.

Although all PIDs are prioritised as Red in the Demand Management Programme, 61 patients (5%) with these disorders were inappropriately assigned a Panel decision of Blue or Grey. This may have been because patients did not meet the criteria specified in the Clinical Guidelines; in this case, a Panel decision of Grey would be appropriate.

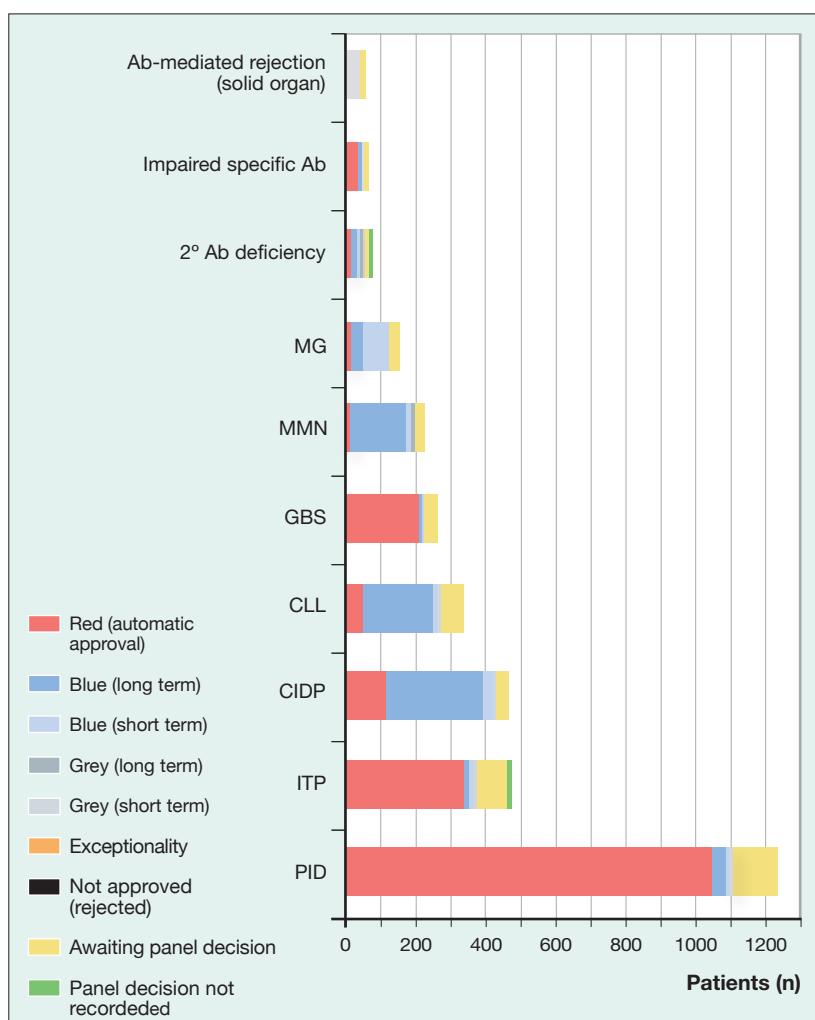
2.5 Immunoglobulin use according to colour-coded prioritisation

The infusion records show that 41% was prescribed under an assigned Panel decision of Red, 40% under a Blue decision (35% long term) and 19% under another Panel decision (Figure 2.5.1). For patient numbers, the proportions are 45%, 29% and 26%, respectively. However, the data available from the database show that not all assigned Panel decisions match the prioritisation defined in the Demand Management Programme. There may be some confusion about the terminology and processes required by the Demand Management Programme. Panels clearly work differently across Trusts, and the interpretation of the guidelines is variable. Some Trusts have agreed with their PCTs that certain grey indications are pre-approved for immunoglobulin prescribing, removing the need for the local Panel to seek approval for each Panel decision for those indications. However,

Table 2.5 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
PIDs	1049	46	7	6	2			126	
ITP	348	10	19		4			89	2
CIDP	116	279	36	2	1			33	
CLL	54	201	17		1			68	
GBS	214	1	8					37	
MMN	8	171	20	1				27	
MG	18	34	78					21	
Secondary antibody deficiencies	22	17	3	19	6			9	2
Impaired specific antibody production	40	15			1			6	
Treatment of acute antibody-mediated rejection following solid organ transplantation	4				1	53		3	

Prioritisation in the Demand Management Programme is shown by shading. For CIDP, the Demand Management Programme prioritises short-term immunoglobulin therapy as Red and long-term therapy as Blue.

**Figure 2.5.2** Number of patients receiving immunoglobulin for individual diagnoses under assigned Panel prioritisation.

For CIDP, immunoglobulin is prioritised as Red for short-term treatment and Blue for long-term treatment. However, Panel decisions were assigned as Blue: short term ($n=36$, 8%), Grey: long term ($n=2$, <1%) and Grey: short term ($n=1$, <1%). GBS is prioritised as Red for short-term treatment, but long-term treatment is not appropriate. However, one patient (<1%) was assigned a Panel decision of Blue: long term and eight (3%) a Panel decision of Blue: short term. Again, it is not clear whether all patients assigned a Panel decision of Red were treated for the appropriate duration.

For ITP, only short-term treatment is appropriate, and is prioritised as Red. However, 10 patients (2%) were assigned a Panel decision of Blue: long term, 19 (4%) were assigned a Panel decision of Blue: short term and four (<1%) were assigned a Panel decision of Grey: short term. For CLL, only long-term treatment is appropriate, and it is prioritised as Blue. However, 54 patients (16%) were assigned a Panel decision of Red, 17 (5%) a Panel decision of Blue: short term and one (<1%) a Panel decision of Grey: long term. Again, it is not clear whether all patients assigned a Panel decision of Red were treated for the appropriate duration.

Two of the top 10 diagnoses were prioritised by the Demand Management Programme as Grey: secondary antibody deficiencies and treatment of acute antibody-mediated rejection following solid organ transplantation. Duration of treatment is not defined in the Clinical Guidelines for 'Grey' conditions. Among the 78 patients with secondary antibody deficiencies, only 25 (about 1/3) were assigned a Panel decision of Grey, while 22 were assigned a Panel decision of Red and 20 a decision of Blue. Most of the 61 patients receiving immunoglobulin to treat acute antibody-mediated rejection following solid organ transplantation were assigned a Panel decision of Grey; only four were assigned an inappropriate Panel decision (all Red).

The DH-sponsored database steering group will look at the best approach to address this confusion. This may involve education (for Panel members, clinicians and/or pharmacists) or alterations to the data entry process. Initial thoughts on the next steps in the development of the database are presented in Chapter 14.

2.6 Recorded immunoglobulin infusion use according to product and manufacturer

Vigam® Liquid is the highest-volume immunoglobulin recorded in the database, reflecting the fact that BPL is the primary contractor in England for the provision of immunoglobulin. The Clinical Guidelines recommend the continuation of brand consistency for patients receiving long-term immunoglobulin, such as those with PID. Future analysis of the data will examine the distribution of 'Red' indications across the different brands to determine if there is sufficient diversity of brand choice at the initiation of long-term treatment. Another

factor that will be reviewed is the brand choice in relation to cost. The cost of immunoglobulin is about £35 per gramme, but there are variations in cost between brands. Although the difference is relatively small, the choice of brand can still have significant impact on the overall immunoglobulin budget, with even a £2-per-gramme difference accounting for many millions difference in total cost.

2.7 Immunoglobulin use in private patients

The intention is that the database will record all immunoglobulin prescribing and thus private patient use should also be entered into the database. There is an entry to allow this to be recorded. Currently, the database has recorded 127 Panel episodes in patients treated privately.

2.8 Recorded use of alternatives prior to request for immunoglobulin

The database gives an opportunity to record alternative therapies tried before immunoglobulin therapy was requested. Although alternatives have been recorded, many appear to be treatments used in addition to immunoglobulin or treatments for comorbid conditions. Alternatives used are discussed in the chapters for each specialism.

2.9 Plasma exchange as an alternative treatment to immunoglobulin

Plasma exchange is an important treatment option in some diseases, particularly in neurology, and some studies show that therapeutic plasma exchange has generally similar efficacy to intravenous immunoglobulin, although some neurologists have concerns that plasma exchange is less safe than immunoglobulin. The database gives an opportunity to record the consideration or use of plasma exchange prior to the request for immunoglobulin therapy.

The database offers a range of entries for plasma exchange ('Tried and failed', 'Considered but patient not suitable', 'Considered but not available' and 'Not applicable')(summary findings in Table 2.9.1), but interpretation of the use, or the efficacy and safety, of plasma exchange is limited by the fact that cases of successful plasma exchange are not recorded. The findings are presented in more detail in Chapter 12.

2.10 Dosing

The Clinical Guidelines do not provide specific dosing recommendations, but note that the normal immunomodulatory dose of 2 g/kg is usually divided into five

Entry	Considered but not available	Considered but patient not suitable	Tried and failed	Not applicable
Patients (n)	119	161	62	3993

Table 2.9.1 Number of patients with an entry for plasma exchange

daily infusions of 0.4 g/kg, although some physicians prefer to use two daily doses of 1 g/kg each. There is considerable interest in the potential benefits of such shorter dosing schedules and this is an area of research interest (see Chapter 13). At the moment, the database infusion records are incomplete and therefore it is difficult to fully interpret the data and not possible to decipher the dosing that has been used. Generally, the infusion data should be interpreted with caution. Data on neurology indications seem to be the most robust in the database, and the dosing data seem reasonable, for example, the average GBS patient dose is 144 g, corresponding to just over 2 g/kg in a 70-kg average person.

2.11 International approaches to immunoglobulin demand management

Managing intravenous immunoglobulin use is a global problem, with Australia, Asia and Pacific nations developing regional guidelines in an attempt to modulate the rapid growth of prescribing. Indeed, in 2005, Australia was the fourth highest user per capita in the world and with annual national increases as high as 15%. In December 2007, the *Criteria for the clinical use of intravenous immunoglobulin in Australia* were developed with contributions from interested parties including the Australian Red Cross Blood Service (ARCBS) under the auspices of the Jurisdictional Blood Committee (JBC). The Criteria document which was approved by the Australian Health Ministers' Conference was implemented nationally in March 2008. These guidelines are broadly similar to the Clinical Guidelines in England, and specify diseases under four categories for immunoglobulin use: established, emerging, and exceptional, and a "not funded" category (indication for which immunoglobulin is not recommended), which is equivalent to Black. Australia has also developed a national immunoglobulin database. Like the National Immunoglobulin Database in England, the national ARCBS Supply Tracking and Reporting System (STARS) database is used to capture individual patient data (including qualifying criteria, dosage regime, treatment response and adverse events) and to generate reports.

A recent review of all existing Western Australian patients showed that the application of the Criteria, with some contribution from lean body weight dose adjustment (reducing the dose in obese patients to allow for the poorly perfused excess adipose tissue), has halted the expected increase in use of immunoglobulin, with a 4% reduction in use. For Australians, this represents saving the plasma from some 13,000 donors and also substantial costs. Of further interest, 54 patients found not

to fulfil the Criteria for continuing immunoglobulin because of diagnoses of IgG subclass deficiencies, all with a history of prolonged severe chest complications, usually under control while on immunoglobulin, had their treatment terminated. None of the stopped patients has restarted immunoglobulin; the few patients where it was felt the risk was too great to consider cessation for re-evaluation continued in a new classification of "existing IgG subclass patients".

2.12 Conclusions

- The 1-year data presented record immunoglobulin use in 5119 patients with a known diagnosis and include a total of 1,168,562 g of immunoglobulin.
- Immunoglobulin volumes described represent the infusions that have been recorded in the database, which are incomplete (~2300 kg allocated by PASA vs. ~1200 kg recorded).
- At the time of data extraction, 161 Trusts had enrolled in the database; of the 168 acute Trusts in England, 12 had not registered for the database.
- Neurological conditions account for more immunoglobulin use than any other specialism (43% by volume); immunology accounts for 31% and haematology/haemato-oncology for 17%.
- The infusion records show that 41% of immunoglobulin was prescribed under an assigned Panel decision of Red, 40% under a Blue decision (35% long-term use) and 19% under another Panel decision; using patient numbers, these figures were 45%, 29% and 26%, respectively.
- PIDs account for the largest number of patients receiving immunoglobulin therapy (1246) and the greatest volume used (295,837 g or 25% of all recorded use); the next greatest volume used is for CIDP (231,694 g or 20% of all recorded use).
- The top 10 diagnoses (by volume) include four neurology indications; there are four 'Red', four 'Blue' and two 'Grey' indications.
- Prescribing in 'Grey' indications amounted to more than 31,000 g; the two high-using 'Grey' indications were secondary antibody deficiencies and antibody-mediated rejection following solid organ transplantation.

- The database records the consideration or use of plasma exchange prior to the request for immunoglobulin therapy, giving a range of choices ('Tried and failed', 'Considered but patient not suitable', 'Considered but not available' and 'Not applicable'), but interpretation of the use, or the efficacy and safety, of plasma exchange is limited by the fact that cases of successful plasma exchange are not recorded.
- The database infusion records are incomplete and therefore difficult to fully interpret; data on neurology indications seem to be the most robust in the database, and the dosing data seem reasonable, for example, the average GBS patient dose is 144 g, corresponding to just over 2 g/kg in a 70-kg average person.
- Managing immunoglobulin use is a global problem, with Australia, Asia and Pacific nations developing regional guidelines in an attempt to modulate the rapid growth of prescribing. In Western Australia, this has halted the expected increase in use of immunoglobulin, with a 4% reduction in use. Insights from the Australian data include the value of considering lean body weight dose adjustment (reducing the dose in obese patients to allow for the poorly perfused excess adipose tissue) and stopping immunoglobulin treatment in patients who do not fulfil the Australian Criteria for continuing immunoglobulin because of diagnoses of IgG subclass deficiencies.

Intravenous and subcutaneous immunoglobulin is an expensive blood product used across a variety of clinical specialities. The criticality and effectiveness of immunoglobulin treatment varies – it is life-saving for some patients for whom no alternative treatment exists, while for other patients, clinically effective and cost-effective alternatives are available. Treatment with immunoglobulin represents a substantial financial commitment for the health service, with an annual cost of about £80 million pounds. Intravenous and subcutaneous immunoglobulin remains a high-cost drug exclusion from the national tariffs and is funded by PCTs, generally without restriction on use (i.e., budgets not capped).

Services involving the use of immunoglobulin (e.g., neurology, immunology and haematology) are generally commissioned by SCGs. The aim of specialised services commissioning is to ensure fair access to clinically effective, first class, standard, specialised services across the country. To this end, the NSCG, on behalf of its 10 SCG members, has recently published a Model Commissioning Policy for immunoglobulin (available to download at www.ivig.nhs.uk).

3.1 Model Commissioning Policy for immunoglobulin

The aims of the commissioning policy closely mirror those of the DH Demand Management Programme for Immunoglobulin. The policy aims to target the scarce supply of immunoglobulin to those patients for whom this treatment is the preferred option and to ensure that immunoglobulin is used in a way that is effective and cost-effective. The commissioning policy requires the operation of a robust mechanism for managing and prioritising access to immunoglobulin treatment at times of short supply (using the colour coding provided in the DH Demand Management Programme to reflect treatment prioritisation – see Terminology of the Demand Management Programme for Immunoglobulin, page x). In addition, the commissioning policy requires that all patient data are entered into the National Immunoglobulin Database, to which funding for immunoglobulin will be tied. As part of this policy, all applications for funding of immunoglobulin, even when retrospectively applied for, should be approved by the provider Trust's

designated immunoglobulin responsible person. All new patients should be logged with the National Immunoglobulin Database and their data provided as required; existing patients should be reviewed and logged on the database during the first 12 months. Under the commissioning policy, all immunoglobulin will be prescribed by a consultant with specialist knowledge of its use; there will be no GP prescribing. A National Immunoglobulin Working Group, which has DH, commissioner and clinician representatives, will provide advice to the NSCG on further development of the service specification.

3.2 National Immunoglobulin Database – linking prescribing with payment

The goal remains that the National Immunoglobulin Database will provide robust data of sufficient quality to allow linking to payments by use. However, there are a number of challenges facing the database before that is possible:

1. The primary limitation at present is that a number of Trusts, including heavy users of immunoglobulin, have not registered on the database. As documented in Chapter 2, 161 were registered on the database, but at least 12 acute Trusts that were unregistered in September 2009.
2. Another difficulty is that the analyses presented in this report are based on the infusion data, which are incomplete in some Trusts. The current estimate is that the database up to September 2009 has captured about 50% of total immunoglobulin use (figure based on PASA estimates of volume of immunoglobulin purchased and distributed and the volume recorded in the database).
3. The identification of the PCT or SHA responsible for the treatment is derived from the GP practice code. At present, only 40% of patients (3651/9088) in the database have a GP practice code recorded. The entry of GP practice code for each patient may become compulsory to ensure accurate linking of treatment costs to the PCT responsible for that patient.

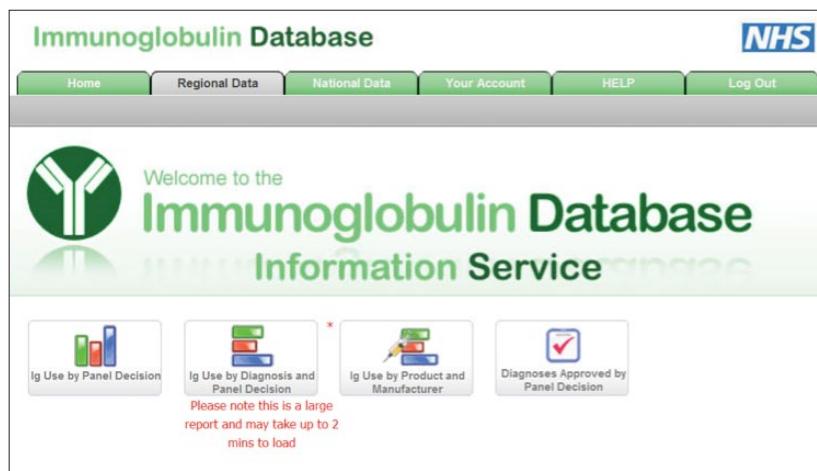


Figure 3.3.1 Commissioner's Database Information Service.

- Finally, the diagnosis upon which the decision to prescribe immunoglobulin is based remains unrecorded, or designated as 'other', in a substantial number of cases and there remains a problem with the number of cases for which the Panel's decision is not recorded. The latter problem will be reduced as a large number of the 'awaiting Panel decision' entries stem from the data migration from the old system, when a problem was discovered in relation to data entry for some patient Panel decisions.

There must be continued improvements in both database function and data entry to ensure the best possible data are available for accurate linking to payments by use. The Model Commissioning Policy states: 'Centres are expected, ***without exception***, to provide a complete dataset to the Department of Health IVIG/SCIG Database in line with information requests from the team overseeing the IVIG/SCIG Database. This will be monitored and ongoing failure to provide data may lead to penalty payments.'

3.3 Commissioner's Database Information Service

As part of the database improvements launched in June 2009, the database was migrated onto the internal NHS N3 network, which uses industry-standard encryption. This has made the system faster and very secure, improving the usability and aesthetics and simplifying the development of future functionality. One of the key additions was the Information Service for Commissioners (Figure 3.3.1).

This facility allows access to data by region, subdivided by centres, according to user name; all users can view reports using national data and filter data using the options provided. Reports are created in the same way as in the main system. The service gives secure real-time online access to reports and charts. It also allows these to be exported for local analysis in a variety of formats including Microsoft Excel, Adobe Acrobat and Microsoft Word.

3.3.1 Analysis of immunoglobulin prescribing in an SHA

An analysis of prescribing in the East of England is presented, with data derived from the Database Information Service. The NHS in the east of England is made up of 41 organisations, including NHS East of England (the SHA), the East of England SCG, 18 acute Trusts and 14 PCTs, which commission care.

Immunoglobulin reporting

The East of England SHA conducted a review of the immunoglobulin data available from the database on 7th August, 2009, which can be used as a benchmark for this analysis conducted on 17th November, 2009. Of the 18 acute Trusts, one Trust (Bedford Hospital NHS Trust) has not registered on the database, and one Trust (West Hertfordshire Hospitals NHS Trust) has registered but entered no data (entering data as this report goes



Figure 3.3.2 The East of England SHA.

to print). In August, both Hinchingbrooke Health Care NHS Trust and West Suffolk Hospitals NHS Trust had not entered data. Although now entering data, their data entry to date is sparse and it is hoped this will improve in the near future.

Immunoglobulin use in individual NHS Trusts

Table 3.3.1 and Figure 3.3.3 show the volumes of immunoglobulin used in individual Trusts. For simplicity, these data exclude the small volumes of immunoglobulin that are recorded as 'returned'. The total volume used (117 kg) represents about 9% of the total use recorded in the database (1270 kg). The estimated immunoglobulin use in the previous analysis used averages across the SHA and estimated overall use at 174 kg. Clearly, all Trusts must enter complete data before an accurate volume of immunoglobulin prescribing can be provided.

Analysis of immunoglobulin use in top 10 diagnoses

The top 10 diagnoses (by volume of immunoglobulin used) in the East of England match closely the national findings, except for MMN. Nationally, the treatment of MMN uses the third highest volume of immunoglobulin, but use is markedly less in the East of England. This may reflect the referral of these rare neurology cases to tertiary referral centres outside this SHA. The volume used in the top 10 diagnoses represents 87% of total volume prescribed. As seen in the national analysis, PID, the neurology indications CIDP, MMN, GBS and MG and the haematology indications autoimmune/idopathic thrombocytopenia purpura (ITP) and CLL make up the vast majority (75%) of immunoglobulin use.

Table 3.3.1 Immunoglobulin use per Trust in East of England SHA

Trust	Volume used (g)
Southend Hospitals NHS Trust	18,439
Cambridge University Hospitals NHS Foundation Trust	17,188
Colchester Hospital University NHS Foundation Trust	15,518
Norfolk & Norwich University Hospital NHS Foundation Trust	11,358
Luton & Dunstable NHS Foundation Trust	10,686
The Queen Elizabeth Hospital Kings Lynn NHS Trust	9877
The James Paget University Hospitals NHS Foundation Trust	7236
Basildon & Thurrock University Hospitals NHS Trust	6637
Papworth Hospital NHS Foundation Trust	4518
Peterborough Hospitals NHS Trust	3682
The Princess Alexandra Hospital NHS Trust	3391
Mid Essex Hospital Services NHS Trust	3051
East & North Hertfordshire NHS Trust	2625
Ipswich Hospital NHS Trust	1975
Hinchingbrooke Health Care NHS Trust	494
West Suffolk Hospitals NHS Trust	144
Total	117,000

The infusion data recorded in the database are incomplete; these data should be interpreted with caution.

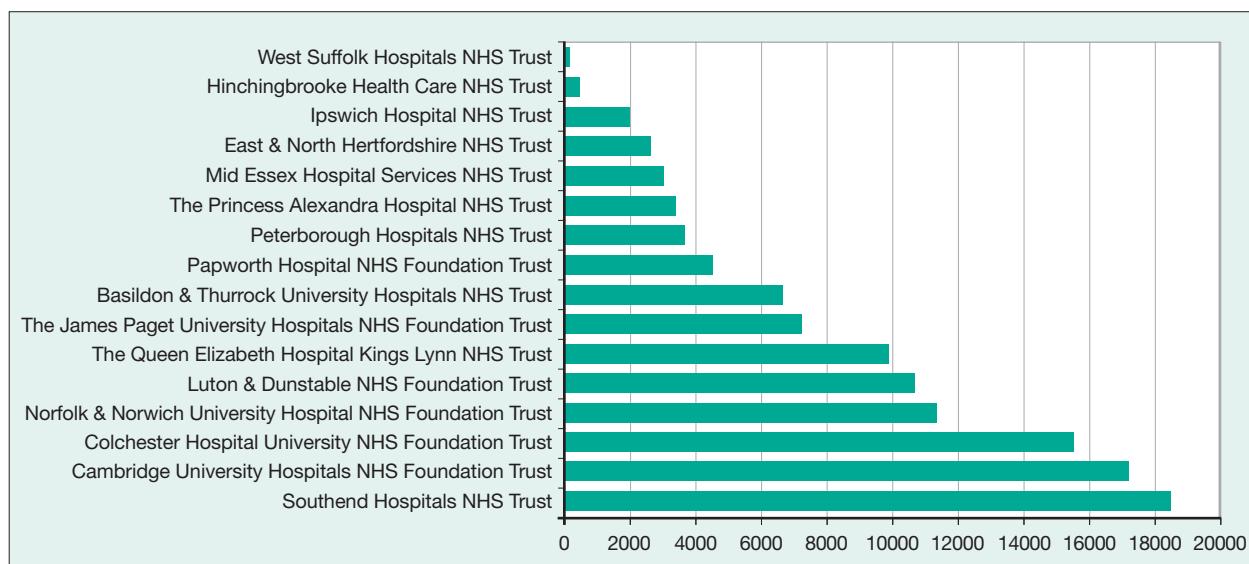


Figure 3.3.3 Immunoglobulin use in individual NHS Trusts in East of England SHA.

A lack of diagnosis (3.6%) and a diagnosis of ‘other’ (7%) account for more than 10% of total usage in the East of England. These findings suggest that changes should be made to the database to ensure that a diagnosis must be recorded for each patient. While the diagnosis of ‘other’ will remain in the database, reflecting the need to record use in diseases that are unlisted in the guidelines because of their rarity, a lack of any diagnosis will be blocked through the introduction of compulsory field completion.

Analysing prescribing according to the assigned Panel decision based on treatment prioritisation colour coding of the DH Demand Management Programme shows that more than 50% of prescribing in the top 10 indications is Red, around 33% is Blue and 2% is Grey, while in about 15% of cases, the Panel decision is outstanding, despite prescription of immunoglobulin. As noted in 3.2, a large proportion of the outstanding Panel decisions relate to data entry problems in the previous version of the database and it is hoped that this issue is resolved going forward.

These findings are valuable from a number of perspectives: they allow an assessment of how much immunoglobulin use could be modulated in the event of a severe supply shortage, and indicate how much immunoglobulin is being used in diseases for which the evidence base for use is weak (Grey). The Database Information Service is designed to allow Commissioners easy access to this information. In diseases prioritised as Blue, an alternative treatment is available and this suggests that large volumes of immunoglobulin could

be made available for the treatment of ‘Red’ indications in the event of a shortage. However, these data are weakened slightly by problems in accurately recording the diseases under the correct treatment prioritisation colour code, which is a consistent finding across the country.

Non-compliance with the Clinical Guidelines

In the East of England, data entry has been largely compliant with the Demand Management Programme, with appropriate colour coding and duration of treatment. The entries for neurology indications are particularly compliant and this reflects the national findings. There are examples of prescribing outside the recommendations of the Demand Management Programme. For example, 320 g of use is recorded as Red for CLL, although the Demand Management Programme prioritises CLL as Blue, reflecting the availability of alternative treatments to manage this disease. Reviewing the total prescribing for the top 10 indications (Table 3.3.2), around 3.8% of prescribing fell outside the Demand Management Programme recommendations.

Immunoglobulin use in diagnoses with lack of evidence of efficacy

(‘Grey’ and ‘other’ indications)

A total of 38 ‘Grey’ indications are listed in the database. For the East of England, use was recorded for 10 of these indications, accounting for 3852 g (around 3% of use in the region). The cost of this prescribing is ~£135,000. The national results from the database (Chapter 2) show that

Table 3.3.2 Volume of immunoglobulin used for top 10 diagnoses under Panel-assigned decision using colour-coded prioritisation

	Red	Blue: long term	Blue: short term	Grey	Awaiting Panel decision	Total (g)
PID	31,475	1465	24	0	3221	36,185
CIDP	4525	11,857	210	0	682	17,274
ITP	8075	80	102	0	1468	9725
CLL	320	7078	300	0	913	8611
Other	860	2513	125	1318	3504	8320
MMN	258	4196	716	0	1307	6477
GBS	5215	0	290	0	256	5761
Diagnosis not recorded	564	439	180	0	3038	4221
MG	407	1284	1329	0	270	3290
Secondary antibody deficiencies	0	515	36	1246	0	1797
Total (g)	51,699	29,427	3312	2564	14,659	101,661

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Colour-coded prioritisation is described in Terminology of the Demand Management Programme for Immunoglobulin, page x.

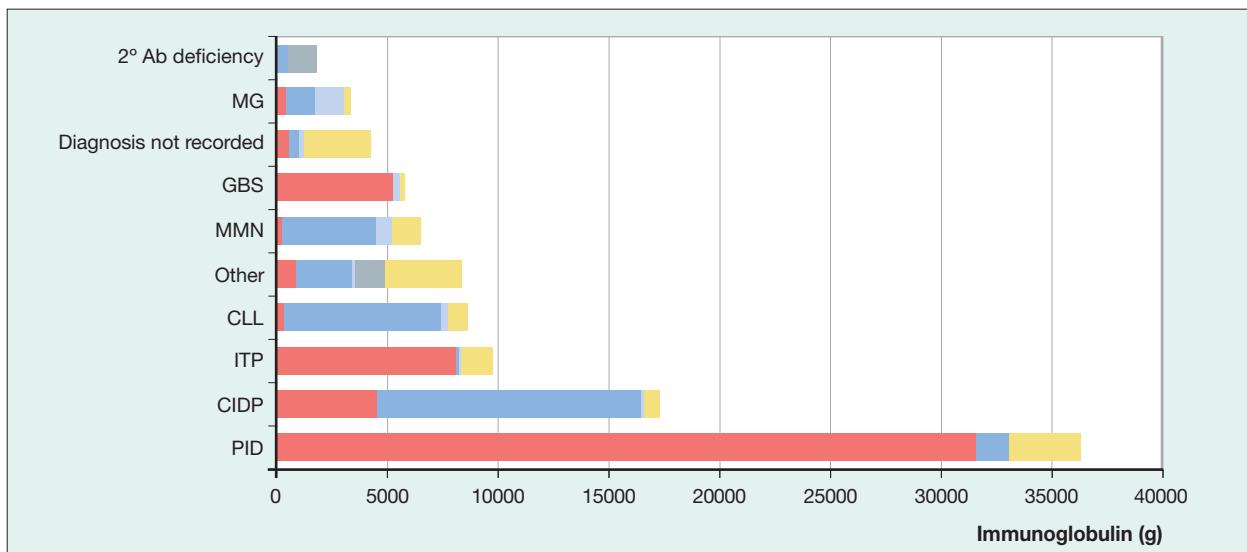


Figure 3.3.4 Volume of immunoglobulin used for top 10 diagnoses under Panel-assigned decision using colour-coded prioritisation. See Table 3.3.2 for colour-coded prioritisation. *The infusion data recorded in the database are incomplete; these data should be interpreted with caution.*

immunoglobulin was prescribed for 25 of these indications and accounts for about 60 kg (5%) of total immunoglobulin use at a cost of ~£2 million. This suggests that 'Grey'-indication prescribing in the East of England SHA is less than the national average.

Immunoglobulin use in diagnoses with evidence of a lack of efficacy ('Black' indications)

A total of 18 'Black' indications are listed in the database. For the East of England, use was only recorded in one 'Black' indication (neonatal sepsis), and two patients received a total of 10 g before the applications were rejected by the local Panel. This suggests that the Panels are functioning well in the East of England and making appropriate, evidence-based decisions. The national results from the database show that immunoglobulin was prescribed for eight 'Black' indications, accounting for about 3.8 kg (0.3%) of total immunoglobulin recorded in the database.

3.4 Immunoglobulin use in diagnoses with lack of evidence of efficacy ('Grey' and 'other' indications)

In certain diseases prioritised as Grey in the Demand Management Programme, the evidence base for efficacy of immunoglobulin is weak, either because the disease is rare or because studies conducted to date have yielded equivocal or contradictory findings. Nationally, around 6% of immunoglobulin was used to treat diseases classified as Grey in the Demand Management Programme (see Chapter 2). The current policy is that patients from this group should be considered on a case-by-case basis and their need prioritised against other competing demands. However, the preferable long-term outcome is

that the evidence base for these diseases is strengthened and the diseases prioritised as Blue or Black.

Two diseases accounted for more than 50% of Grey use: secondary antibody deficiencies and the treatment of acute antibody-mediated rejection following solid organ transplantation. For Commissioners to consider reclassifying these indications, the following parameters are required: the health gain expected with immunoglobulin therapy, the evidence on which this gain is based, a clear definition of the disease, the numbers expected to be prescribed immunoglobulin and the approximate immunoglobulin requirement per patient as a measure of cost.

3.5 Discussion

There has been considerable expansion of the clinical situations in which immunoglobulin is used in recent years. Some of this has been done in the absence of robust evidence and little in the way of assessment of value for money. In addition, there is variable clinical practice in this area. These factors, taken together with the limit in supply, have created a situation where it is particularly important that Commissioners have clearly defined policies about access to immunoglobulin and robust data of immunoglobulin prescribing at a national level.

This first report from the National Immunoglobulin Database begins to form a picture of how immunoglobulin is being prescribed. The data clearly show that improvements are required before the database is sufficiently robust to be able to link to payments by use. Key issues include the need for all Trusts to register and enter data, and the need to enter data that reflect the DH Demand Management Programme and model commissioning policy, in particular addressing the issue of inappropriate use of the Red/Blue/Grey designations.

Immunology

Alison Jones and Carrock Sewell

CHAPTER 4

Immunoglobulin replacement is the mainstay of treatment for patients with PIDs. The efficacy of immunoglobulin in established PIDs is supported by a strong evidence base provided by retrospective surveys and controlled studies (level IIb evidence). No alternative is available in patients who have clear-cut established PID, which is therefore prioritised as Red by the National Demand Management Programme.

Primary immunodeficiencies

The PIDs have been sub-divided into a number of categories that at present are not clearly defined, but are intended to reflect diagnoses as follows:

- i. 'CVIDs' should include all patients diagnosed with CVID according to the criteria established by the European Society for Immunodeficiency.
- ii. 'Severe humoral immune deficiency' includes various forms of severe pure antibody deficiency. Most of these patients are affected by X-linked agammaglobulinaemia, but a small number have other autosomal recessive disorders of B-cell development or function.
- iii. 'Hypogammaglobulinaemia' is a poorly defined category that may include a variety of disorders. This category may include patients who do not fulfil the criteria for CVID and do not have a clear-cut pure B-cell defect, but have low immunoglobulin levels as a result of another primary underlying disorder. Some of these may be children with maturational low immunoglobulin levels in whom the use of immunoglobulin will not be lifelong, but will be medium to long term.
- iv. 'Primary immunodeficiencies' is intended to encompass patients with severe complex primary immunodeficiency requiring BMT or gene therapy. This includes all infants with severe combined immunodeficiencies and other complex combined immunodeficiencies.
- v. 'Hyper IgM syndromes' are a range of defects of immunoglobulin class-switching that result in

functional immunoglobulin deficiency. The most frequent of these is CD40 ligand deficiency, or X-linked hyper-IgM syndrome.

Because of the lack of clarity, it is not possible to ascertain at present whether PID patients have been entered into appropriate categories in the database, but all PIDs should be assigned a Panel decision of Red.

Specific antibody deficiency

This refers to patients who have normal or slightly low immunoglobulin levels but are unable to mount specific antibody responses to polysaccharide antigens and suffer severe recurrent infections. The evidence for efficacy in these patients is less strong (level III). These patients may require immunoglobulin replacement but alternatives are effective in some. Therefore, this condition is prioritised as Blue by the National Demand Management Programme, despite the fact that it is a PID.

Secondary immunodeficiency

This category includes immunoglobulin deficiency following BMT for non-immunodeficiency disorders (prioritised as Red by the National Demand Management Programme), drug-induced hypogammaglobulinaemia (prioritised as Grey) and HIV disease in children (prioritised as Black). All patients with secondary immunodeficiency are currently entered into a single category, so distinction between the different underlying causes is not possible.

Kawasaki disease

This vasculitic disorder is prioritised as Red by the National Demand Management Programme, with a strong evidence base for efficacy. Immediate therapy with immunoglobulin is superior to any alternative.

4.1 Immunoglobulin use in immunology compared with national immunoglobulin use

Historically, it has been estimated that PID has accounted for approximately 30% of immunoglobulin use. Data accumulated in the National Immunoglobulin Database so far

Diagnosis	n	Volume (g)	Average dosage (g/patient)
Primary immunodeficiencies	1222	292,146	239
Secondary antibody deficiencies	77	20,326	264
Impaired specific antibody production	60	10,406	173
Kawasaki disease	101	3656	36
Immunodeficiency secondary to paediatric HIV infection	1	20	
Other (Immunology)	101	20,778	205
Total	1562	347,332	

Table 4.2 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading

indicate that immunology indications account for 30.8% of total use by volume, with PID collectively accounting for at least 87% of this (28.3% of national total). This suggests that the data are a reasonable reflection of the actual distribution of usage nationally, even though significant numbers of Trusts have not so far contributed data.

4.2 Immunoglobulin use for individual diagnoses

Given the lack of clarity regarding which diagnostic category patients may have been assigned to, the data for PID may be best considered collectively, in which case, including hyper-IgM syndrome and severe humoral immunodeficiency, all established PID accounts for 1222 patients (22% of all patients). The total dose given in these patients is around 292 kg, averaging 240 g/patient/year. This is lower than the predicted average dose of 360 g/year (30 g monthly for a 60-kg individual), but a significant proportion of use is in the paediatric population, where doses are much lower. This figure is also compromised by incomplete infusion data.

Patients with specific antibody deficiency may require immunoglobulin replacement if infections cannot be prevented with prophylactic antibiotics, and if there is a risk of development of lung damage. A total of 60 patients with specific antibody deficiency are recorded in the database.

Overall, 77 patients with secondary antibody deficiency have been reported. There is no indication whether these patients have antibody deficiency secondary to BMT for malignancy, CLL or drugs. It is important to be able to make these distinctions in the future because they fall within different priority groups in the Demand Management Programme.

4.3 Immunoglobulin use according to colour-coded prioritisation

The Demand Management Programme defines the priority of immunoglobulin therapy for PID as Red. Therefore, for all patients with established PID, Panels should assign decisions of Red. The data show that this has been done for most patients, but significant numbers

Table 4.3 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
Primary immunodeficiencies	1049	46	7	5	2			126	
Impaired specific antibody production	40	15			1			6	
Secondary antibody deficiencies	22	17	3	19	6			9	2
Kawasaki disease	93		1					7	
Other (Immunology)	75	4	3	1	3	1		14	

Prioritisation in the Demand Management Programme is shown by shading.

are wrongly assigned (46 Blue: long term, 7 Blue: short term, 6 Grey: long term and 2 Grey: short term). Patients with PIDs all require long-term use, which in the majority will be lifelong. A small group of children with transient hypogammaglobulinaemia are able to discontinue treatment when endogenous immunoglobulin production normalises.

The Demand Management Programme defines the priority of immunoglobulin therapy for specific antibody deficiency as Blue. Although Panels should therefore assign decisions of Blue, most assigned Panel decisions are Red (40/62). The next iteration of the Clinical Guidelines needs to consider the prevailing view that specific antibody deficiency is in fact a PID and hence, in the future, this may be prioritised as Red.

The extracted data for secondary antibody deficiencies do not allow distinction between those with antibody deficiency following BMT for malignancy (Red: short term), CLL (Blue: long term) or drug-induced or other causes of hypogammaglobulinaemia (Grey).

Most children with Kawasaki disease have been assigned an appropriate Panel decision of Red (93/101). All these will have required short-term use.

Of the 101 patients with a listed diagnosis of 'other', 74 have been assigned a Panel decision of Red, suggesting that most are likely to be affected by PID. One of these patients has been authorised under exceptionality. In the absence of diagnostic information, no comment is possible.

4.4 Immunoglobulin use in diagnoses with evidence of a lack of efficacy ('Black' indications)

The only immunology diagnosis where immunoglobulin is clearly not recommended is immunodeficiency secondary to paediatric HIV infection. Only one such patient is recorded as having received immunoglobulin. This patient is also recorded as having received steroids as an alternative, which suggests that the immunoglobulin was being used as an immunomodulator rather than as replacement. No Panel decision for this patient appears in the data.

4.5 Recorded use of alternatives prior to request for immunoglobulin

To reiterate, for the large majority of immunology patients, there are no alternatives as immunoglobulin is replacement therapy. For specific antibody deficiency and secondary antibody deficiency, antibiotics may be an initial alternative, and for Kawasaki disease steroids may be used but would rarely be considered an alternative. Steroids and other immunosuppressive agents are used to treat autoimmune or inflammatory complications of PID, but these would never be an alternative to immunoglobulin.

In 48 patients with PID, 11 with specific antibody deficiency and nine with secondary antibody deficiency, 'other' alternatives are recorded. These are most likely to be prophylactic antibiotics. In most cases of established PID, this is not a true alternative and is more likely to be additional treatment where patients already have complications such as bronchiectasis.

4.6 Recorded consideration of plasma exchange prior to request for immunoglobulin

Plasma exchange is not an alternative to immunoglobulin for almost all immunology patients.

4.7 Conclusions

- Immunology disorders accounted for 30% of total national immunoglobulin usage.
- PIDs account for the vast majority and, as expected, the most frequent indication is CVID.
- The diagnostic categories within PID are currently poorly defined and confusing, and it is therefore not possible to interrogate the database regarding use of immunoglobulin in other individual PIDs.
- For the most part, PID patients have been appropriately assigned a Panel decision of Red.
- There is virtually no evidence of inappropriate use of immunoglobulin (1 patient with HIV disease).
- The distribution of usage appears to reflect previous estimates of national usage, but the overall data are incomplete, due to Trusts not yet entering data and incomplete infusion data from those that are.
- In most areas, there is good consensus regarding the allocation of priority groups, reflected in the mainly appropriate Panel decisions.
- In the case of specific antibody deficiency, opinions vary: some immunologists believe that it should be prioritised as Red, even though strong evidence is lacking.
- Cumulative information collected in the database regarding outcomes in patients with specific antibody deficiency treated with immunoglobulin should, in time, provide more robust evidence regarding efficacy, as will be the case for many of the current 'Blue' and 'Grey' indications.

CHAPTER
5

Haematology

Jennie Wimperis

The Deloitte survey commissioned by the DH in June 2006 estimated that 18% of immunoglobulin use in the UK was for the treatment of haematological diseases (both malignant and non-malignant), thus identifying haematology as a major immunoglobulin user (see Chapter 2). The data presented in this chapter bear this out; the National Immunoglobulin Database shows that non-malignant haematology indications account for 10% of the total use of immunoglobulin by volume and malignant haematology for 8% (see Chapter 4), making the haematology specialism the third largest user of immunoglobulin.

The 2006 survey revealed that the primary indication for immunoglobulin in non-malignant haematology is treatment of autoimmune/idiopathic thrombocytopenia purpura (ITP). This is confirmed by the extracted data, in which ITP accounted for 58% of the total volume of immunoglobulin used in haematology, making it the fifth highest user of all the listed diagnoses. The Clinical Guidelines recommend that all immunoglobulin use in non-malignant haematology should be short term. Although this is largely borne out by the database, there are a number of cases of long-term use in ITP; more is presented on these long-term cases in 5.3. ITP also affects children, but few children (40) received immunoglobulin, and almost all the treatment was short term. The next largest reported uses of immunoglobulin were treatment of autoimmune haemolytic anaemia and alloimmune thrombocytopenia.

A troubling feature of the data in this first year is the large numbers of patients for whom the diagnosis was specified as 'other'. The original intention was that the diagnosis 'other' be reserved for cases of rare diseases not specified in the Clinical Guidelines. These cases should be treated on a case-by-case basis and should be treated as 'Grey' indications, with the decision to treat therefore falling to the local Panel in conjunction with the local commissioning body. The data show that this has been a particular problem in the haematology specialism. Of the 195 patients with a diagnosis of 'other (haematology)', only 12 were assigned a Panel decision of Grey (these are reviewed in detail in 5.3), 56 of Red and 89 of Blue. The volume used in these 'other' diagnoses was high, at around 25 kg. In 81 cases, use was recorded as long term.

Such incorrect assignment of the colour-coded prioritisation defined in the Demand Management Programme is a consistent finding in the haematology specialism. For example, there are three cases of immunoglobulin use in ITP that have been assigned a Panel decision of Grey. It is unclear whether this reflects database entry errors or a fundamental misunderstanding of the colour-coded prioritisation in the Demand Management Programme.

5.1 Immunoglobulin use in haematology compared with national immunoglobulin use

In total, 801 haematology patients used 113,310 g of immunoglobulin in the 12-month period under review. As shown in Chapter 2, this accounts for 16% of the patients receiving immunoglobulin and 9.7% of the product used nationally.

5.2 Immunoglobulin use for individual diagnoses

Short-term treatment of ITP is the only haematology disease for which prioritisation in the Demand Management Programme is Red. This reflects that in certain cases, the degree and severity of thrombocytopenia is life threatening and therapeutic intervention with immunoglobulin is potentially lifesaving, with no equivalent alternative treatment available. The ability of immunoglobulin to increase the platelet count in ITP is supported by numerous studies and, importantly, there are randomized data confirming the advantage of immunoglobulin over systemic corticosteroids.

Of the other haematology indications, the largest indications are autoimmune haemolytic anaemia and alloimmune thrombocytopenia. For all other indications, the volume of use was small. For indications with no clear evidence for efficacy (prioritised as Grey in the Demand Management Programme), use accounted for only 1.2% of total volume.

Table 5.2 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

Diagnosis	n	Volume (g)	Average dosage (g/patient)
Autoimmune/idiopathic thrombocytopenia	432	67,377	156
Autoimmune haemolytic anaemia	42	5779	138
Alloimmune thrombocytopenia - fetal therapy (treatment to the mother)	7	3077	440
Alloimmune thrombocytopenia - neonatal therapy	14	2598	186
ITP (<16 years)	40	1942	48
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	16	1395	7
Evans' syndrome	7	1377	196
Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)	4	875	219
Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome	15	864	58
Adult HIV-associated thrombocytopenia	6	815	86
Acquired red cell aplasia due to parvovirus B19	6	581	97
Acquired von Willebrand disease	3	485	162
Systemic lupus erythematosus with secondary immunocytopenias	5	480	96
Aplastic anaemia/pancytopenia	3	265	88
Post transfusion purpura	3	147	49
Autoimmune (acquired) haemophilia	1	140	140
Autoimmune neutropenia	1	90	90
Acquired red cell aplasia NOT due to parvovirus B19	1	72	72
Other (Haematology)	195	24,953	128
Total	801	113,312	

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.

5.3 Immunoglobulin use according to colour-coded prioritisation

The data in Table 5.3 show that a proportion of decisions assigned by Panels are not in keeping with the colour-coded prioritisation in the Demand Management Programme. Although indications designated as Red, such as ITP, are pre-approved for immunoglobulin use without the need for formal Panel approval, the appropriate Panel decision should still be recorded in the database.

Further investigation of the seven cases of long-term use in adults with ITP was warranted, given that ITP treatment with immunoglobulin is usually reserved for acute episodes. This use seemed reasonable as there may be rare cases of ITP that are rapidly relapsing and

require several courses of immunoglobulin to prevent acute bleeding events. Additional data were available for six of the seven cases. The volume of immunoglobulin used (2655 g) was largely accounted for by one patient who was given more than 2300 g over the 1-year period under review. Of the remaining five cases, the volume of immunoglobulin provided per course was low: one patient was given six courses over a 6-month period; another patient received 10 courses over a 1-year period, another four courses over a 9-month period and another three courses over a 4-month period; in one case, the dates of infusion were not recorded correctly. Although long-term use is not recommended, these data show that there is no significant long-term use of immunoglobulin for ITP.

Table 5.3 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
ITP - adult	320	7	19		4			80	2
Autoimmune haemolytic anaemia	5	5	23		1			8	
ITP (< 16 years)	28	3						9	
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	1		9					6	
Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome		1	8				1	5	
Alloimmune thrombocytopenia - neonatal therapy	13							1	
Alloimmune thrombocytopenia - fetal therapy (treatment to the mother)	5							2	
Evans' syndrome	1	1	4					1	
Acquired red cell aplasia due to parvovirus B19			4					2	
Adult HIV-associated thrombocytopenia		1	3					2	
Systemic lupus erythematosus with secondary immunocytopenias	2				1			2	
Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)				1	1	2			
Acquired von Willebrand disease						3			
Aplastic anaemia/pancytopenia		1						2	
Post transfusion purpura	1		2						
Acquired red cell aplasia NOT due to parvovirus B19								1	
Autoimmune (acquired) haemophilia		1							
Autoimmune neutropenia			1						
Other (Haematology)	56	81	8	5	7			37	1

Prioritisation in the Demand Management Programme is shown by shading.

There were three cases of paediatric ITP for which the assigned Panel decision was long-term treatment. The ages of the children were 0 (neonatal case), 5 and 11 years. The neonatal case was treated over a 6-week period, the 5-year-old was given treatment over an extended period (October 2008–September 2009) and the 11-year-old received treatment over a 1-month period. This confirms that long-term use of immunoglobulin in paediatric ITP is extremely rare and suggests that only one case was entered correctly into the database.

Of the 17 patients who received immunoglobulin for 'Grey' indications, SLE with secondary immunocytopenias accounted for the largest number of patients, although this ($n=5$) and the volume used (480 g) were small. Again, the Panel decisions assigned for 'Grey' indications are largely incorrect, with only 4/13 patients correctly assigned a Grey Panel decision.

Of the 195 patients with a diagnosis of 'Other (haematology)' (i.e., conditions not listed in the Clinical Guidelines), which are prioritised by the Demand Management

Programme as Grey), 12 were assigned a Panel decision of Grey; individual patient records were reviewed. In the five cases of long-term use, two cases were correctly reported: one case each of IPEX syndrome and antiphospholipid syndrome, neither of which is listed in the Clinical Guidelines. Although IPEX syndrome is a PID, replacement immunoglobulin is only required post-transplant. The other three long-term uses were incorrectly recorded under 'other (haematology)': one case each of Hodgkin's disease, chronic graft versus host dis-

ease after MUD BMT and antibody deficiency secondary to CLL. Of the seven cases of short-term use, one was also entered as long-term use (IPEX), one was recurrent infection following allogeneic BMT, one was a PID patient and one was recurrent infection post-chemotherapy. In three cases, there was no clue as to the disease being treated. These results suggest that there is a major issue with assignment of Panel decision and that forced entry into the correct category should be introduced to improve data quality.

Table 5.4 Volume of immunoglobulin used for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
ITP - adult	46,122	2655	4337		409			13,225	630
Autoimmune haemolytic anaemia	740	660	3089		72			1218	
Alloimmune thrombocytopenia - fetal therapy (treatment to the mother)	2447							630	
Systemic lupus erythematosus			35	1150	642			843.5	50
Alloimmune thrombocytopenia - neonatal therapy	2558							40	
ITP (< 16 years)	1540	130						272	
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	3		60					1333	
Evans' syndrome	250	120	581					426	
Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)			30	648	198				
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome		33	382				50	400	
Adult HIV-associated thrombocytopenia		210	295					310	
Acquired red cell aplasia due to parvovirus B19			391					190	
Acquired von Willebrand disease					485				
Systemic lupus erythematosus with secondary immunocytopenias	102				150			228	
Aplastic anaemia/pancytopenia		80						185	
Post transfusion purpura	100		47						
Autoimmune (acquired) haemophilia		140							
Autoimmune neutropenia			90						
Acquired red cell aplasia NOT due to parvovirus B19								72	
Other (Haematology)	6977	11,465	435	1130	325			4600	23

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.

Table 5.5 Recorded use of alternatives prior to request for immunoglobulin in individual diagnoses

Diagnosis	Cyclophosphamide	Methotrexate	Corticosteroids	Rituximab	Ciclosporin	Other
ITP - adult	6		197	43	11	51
Autoimmune haemolytic anaemia	3		23	8	3	2
ITP (< 16 years)			8	1		2
Evans' syndrome	1		5	2		1
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome			3		3	2
Systemic lupus erythematosus with secondary immunocytopenias	1		2	1		1
Acquired red cell aplasia NOT due to parvovirus B19			1	1		
Alloimmune thrombocytopenia - neonatal therapy						2
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)						2
Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)			2			
Acquired red cell aplasia due to parvovirus B19						1
Adult HIV-associated thrombocytopenia						1
Alloimmune thrombocytopenia - fetal therapy (treatment to the mother)			1			
Autoimmune neutropenia						1
Other (Haematology)	4		13	5		25

5.4 Estimates of immunoglobulin doses used

Reviewing the volumes used gives some clues to the dosing employed, but the dosing data are incomplete. For ITP, 46,121 g were used in 320 adult patients with an assigned Panel decision of Red. The average dose of immunoglobulin per person was 144 g, which equates to an average of about 2 g/kg in a 70-kg patient. Although standard dosing comprises a single dose of 2 g/kg given over 5 days, there has been a move towards giving the dose over a shorter timeframe, but the data do not allow further investigation. The average dose for adult ITP patients awaiting Panel decision is higher (165 g), which might imply that these cases were more complex, but it is difficult to be sure, especially given the incomplete infusion data. In paediatric patients, 1539 g were used in 28 cases assigned a Panel decision of Red. The average dose of immunoglobulin per child was 55 g, which equates to an average of about 2 g/kg in a 27-kg patient.

5.5 Recorded use of alternatives prior to request for immunoglobulin

As expected, corticosteroids are the primary alternative treatment used. This is particularly the case in ITP, with 197 patients receiving corticosteroid treatment. The only products with market authorisation currently available for the treatment of ITP are corticosteroids and immunoglobulin; anti-D is no longer available (WinRho® SDF was withdrawn in August 2009, and other products are not licensed for the treatment of ITP). Other treatments in regular use include immune suppression (azathioprine, mycophenolate, cyclosporin), danazol, dapsone and cytotoxics (cyclophosphamide, vinca alkaloids). More recently, use has been considered of B lymphocyte depletion with the monoclonal anti-CD20 antibody rituximab and thrombopoietin agonists (eltrombopag and romiplostim).

5.6 Recorded consideration of plasma exchange prior to request for immunoglobulin

The use of plasma exchange has been extremely limited, reflecting both the limited value of plasma exchange in haematology and the limited and fragmented availability of plasma exchange services throughout the country. It was considered in a total of 24 patients, of whom 12 were deemed unsuitable and six failed a trial of plasma exchange; plasma exchange was not available for the remaining six. Of these 24 patients, none had a diagnosis for which plasma exchange is recommended as an alternative, although two had a diagnosis of 'other'.

5.7 Conclusions

- Immunoglobulin use in non-malignant haematology is driven by ITP, an indication for which use is appropriate and can be life saving in cases of profound thrombocytopenia.
- Treatment with immunoglobulin in other haematology indications accounted for a very small proportion of national use.
- There was minimal use in 'Grey' indications, although most prescribing is not supported by appropriate Panel decisions.
- Reflecting on future use of immunoglobulin for ITP treatment, important changes in the availability and perceived safety of alternatives might be expected to have an impact on immunoglobulin prescribing, with the withdrawal of anti-D in August 2009 and concern regarding the increasingly reported association between rituximab and progressive multifocal leukoencephalopathy.
- Alternatives with a different mode of action (thrombopoietin receptor agonists) are now being licensed (e.g., romiplostim). Although these agents will be used for the management of chronic ITP, their use may have some impact on the volume of immunoglobulin used for the management of ITP, for example, removing the need for short-term immunoglobulin for patients undergoing surgery.

The National Immunoglobulin Database reveals that 'haemato-oncology' is a significant user of immunoglobulin. The primary indication for immunoglobulin in malignant haematology was CLL, which accounted for 55% of the immunoglobulin use in the specialism. In CLL, immunoglobulin is indicated for prophylaxis against infection in the context of recurrent infections, despite immunisation and the use of prophylactic antibiotics. Overall, 82% of all usage was for an infective indication. The 'other (haem-oncology)' diagnosis accounted for 13% of all patients; review of the actual indications in this category shows that a diagnosis of lymphoma was common. This raises an important issue for review in the next iteration of the Clinical Guidelines: the use of immunoglobulin in other chronic lymphoproliferative disorders such as non-Hodgkin's lymphoma. Of the remaining 31 patients (5%), only seven (1%) were given immunoglobulin for a diagnosis prioritised as Black by the Demand Management Programme (autologous BMT). Overall, the data show a pattern of use that appears to

be appropriate, largely for infective indications, with no significant use in 'Black' indications.

6.1 Immunoglobulin use in haemato-oncology compared with national immunoglobulin use

In total, 623 haemato-oncology patients used 78,398 g of immunoglobulin in the 12-month period under review, accounting for 12% of patients and 6.4% of the product used nationally.

6.2 Immunoglobulin use for individual diagnoses

CLL, MM, low serum IgG levels following HSCT for malignancy and infection following allogeneic BMT or HSCT account for 82% of all usage in haemato-oncology.

Diagnosis	n	Volume (g)	Average dosage (g/patient)
CLL	341	47,374	139
MM	91	10,330	114
Low serum IgG levels following HSCT for malignancy*	56	3773	67
Infection following allogeneic BMT or HSCT	20	1986	99
Graft versus host disease following allogeneic BMT or HSCT	9	1219	135
Autologous BMT	936	134	
Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome	15	864	58
Other (haem-oncology)	84	11,917	142
Total	623	78,398	

Table 6.2 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.
*Red for short-term therapy but Blue for long-term therapy.

Overall, the average usage per patient for these diagnoses varies from 67 to 140 g. For CLL, the 140 g/patient is hard to interpret. Assuming an average patient weight of 70 kg and a 0.25-g/kg dose, this implies patients received a mean of eight courses. Administration in this indication is usually at 4-weekly intervals, which may indicate that many patients are 'rested' over the summer months. However, given the incompleteness of the infusion data recorded, it is difficult to interpret these average doses with confidence.

The picture for MM is similar, with an average immunoglobulin dose per patient of 113 g. The average immunoglobulin dose per patient for low serum IgG levels following HSCT for malignancy was only 67 g. This is in keeping with the recommendation of short-term treatment in the Clinical Guidelines, prioritised as Red by the Demand Management Programme: the assigned Panel decisions are almost all Red and the dosing suggests no long-term administration. In haemophagocytic lymphohistiocytosis/haemophagocytic syndrome, the average dose was the lowest at 58 g/patient, which is in keeping with the expected younger age and lower weights of these patients and a single episode of administration. Again, this is in keeping with the Clinical Guidelines, where long-term use is not recommended.

6.3 Immunoglobulin use according to colour-coded prioritisation

The only diagnosis in haemato-oncology prioritised as Red by the Demand Management Programme is low serum IgG levels following HSCT for malignancy, and

most of the available Panel decisions (23/30) were correctly assigned as Red. However, a further 94 Panel decisions in patients with other diagnoses were assigned as Red, which is clearly incompatible with the Demand Management Programme. Even if these cases (largely for CLL and MM) really were situations where life-threatening complications would have developed without treatment, this has no bearing on the prioritisation assigned by the Demand Management Programme and such cases should be recorded accurately in the database according to their defined prioritisation. Overall, the assigned Panel decisions show significant variation from the guidance and analysis of individual cases would be required to understand to what degree this is due to poor data recording or misunderstanding of the roles and processes required by the Demand Management Programme. Interestingly, the seven cases of immunoglobulin use for autologous BMT, a 'Black' indication, were all reviewed and approved at a Panel hearing.

A total of 113 patients received immunoglobulin for diagnoses prioritised as Grey by the Demand Management Programme (including 'other (haem-oncology)'). This constitutes 18% of the haemato-oncology patients in the database and 19% of the use by volume. Panel decisions are available for 79, with most (66/79, 84%) assigned a Panel decision of Red or Blue, again suggesting major divergence between the decision-making process and the colour-coded prioritisation of the Demand Management Programme. However, further analysis of these cases suggests that at least some of the Panel decisions were correct, with incorrect disease data entered. For example, there were two cases of CLL and five cases of primary immunodeficiency with concomitant

Table 6.3.1 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
CLL	54	201	17		1			68	
MM	10	65	4					12	
Low serum IgG levels following HSCT for malignancy*	23	3	2	1			1	26	
Infection following allogeneic BMT or HSCT	3	1	2	1	3			10	
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome		1	8				1	5	
Graft versus host disease following allogeneic BMT or HSCT	4			2	1			2	
Autologous BMT	2	3			1	1			
Other (haem-oncology)	21	30	5	1	4	1		22	

Prioritisation in the Demand Management Programme is shown by shading. *Red for short-term therapy but Blue for long-term therapy.

Table 6.3.2 Volume of immunoglobulin used for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
CLL	8343	30,048	1472		30			7481	
MM	1382	7908	120					920	
Low serum IgG levels following HSCT for malignancy*	1961	490	238	200			25	860	
Infection following allogeneic BMT or HSCT	235	270	180	200	238			863	
Graft versus host disease following allogeneic BMT or HSCT	619			505	25			70	
Autologous BMT	274	322			25	315			
Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome		33	382				50	400	
Other (haem-oncology)	2549	5465	640	400	185	125		2553	

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading. *Red for short-term therapy but Blue for long-term therapy.

malignant disease (MM, non-Hodgkin's lymphoma or acute lymphoblastic leukaemia). Most significantly, there were 28 cases of lymphoma, mainly non-Hodgkin's lymphoma, which should be assigned a Panel decision of Grey as they are not listed in the Clinical Guidelines. This suggests that the management of lymphoma, particularly B-cell non-Hodgkin's lymphoma, should be included at the next guideline review.

6.4 Recorded use of alternatives prior to request for immunoglobulin

The use of immunoglobulin in the haemato-oncology indications will, in most cases, be for infective reasons. In this context, the 'alternatives tried' are not meaningful as the listed options are not used to treat or prevent infection and probably represent concomitant treatment with chemotherapy/immunosuppressants for other reasons. The single largest category of alternatives to immunoglobulin is 'other' ($n=73$), and it would be useful to analyse this further to determine whether this is use of prophylactic antibiotics and immunisation in the appropriate settings.

6.5 Recorded consideration of plasma exchange prior to request for immunoglobulin

Plasma exchange was reported to be used in one case only, in a patient with CLL. As the use of immunoglobulin in haemato-oncology is largely for infective causes

associated with immunodeficiency, either inherent to the disease process and/or to chemo-immunotherapy, plasma exchange does not have a role in this setting.

6.6 Conclusions

- Immunoglobulin prescribed for haemato-oncological indications accounts for 12% of patients in the database, but only about 6.4 % of use by volume.
- Most use is for CLL (55%), followed by MM (15%), for both of which there are supportive RCTs, then low serum IgG levels following BMT or HSCT (9%) and infection following allogeneic BMT or HSCT (3%).
- The long-term use of immunoglobulin in CLL together with the average dose suggests that, on average, patients are receiving eight infusion episodes per year, compatible with a 'rest' period over the summer months, but the incomplete infusion data should be interpreted with caution.
- The only 'Red' indication, low serum IgG levels following HSCT for malignancy, was assigned as such in most Panel decisions and this use appears to be in keeping with the Clinical Guidelines (i.e., short-term administration).
- Use in diagnoses prioritised as Grey by the Demand Management Programme (including 'other (haem-oncology)') was significant, accounting for 18% and 19% of patients and volume, respectively, with most

- assigned a Panel decision of Red or Blue. Further review showed at least some of the Panel decisions were correctly recorded, due to incorrect disease data entry.
- Given the large volume of use in lymphoma, particularly non-Hodgkin's lymphoma, the use of immunoglobulin in other lymphoproliferative malignancies should be examined in the next iteration of the Clinical Guidelines.
 - Use in conditions prioritised as Black by the Demand Management Programme (autologous BMT) was minimal, with seven patients (1%) receiving immunoglobulin for this indication.
 - Overall, the data suggest appropriate use of immunoglobulin in most recorded cases. Evolution of the database, along with further education with respect to data quality and the Panel decision-making process, are important next steps.

Before the institution of the National Immunoglobulin Database, neurology was known to be a heavy user of immunoglobulin and there was concern about the proliferation of usage for large numbers of rare and unusual diagnoses, where the evidence base for efficacy was not strong, or was positively lacking. The data contained within this chapter demonstrate that this is not the case. Usage is in general appropriate and supported by good evidence for the majority of uses; a number of rare indications exist but immunoglobulin use in these conditions is uncommon.

The use of immunoglobulin for neurological indications accounts for more than 40% of the total usage of immunoglobulin and 25% of all patients receiving treatment, making neurology the largest individual specialism user. It also has the greatest number of indications for treatment, of which four indications account for 85% of all patients treated and 87% of the immunoglobulin given to neurology patients. The use of immunoglobulin in these four indications is supported by RCT evidence, which for CIDP, GBS and MMNCB is of high quality.

Of the remainder of the neurological diagnoses entered into the database, 5% of patients have diagnoses that are rare but for which use is supported by at least some case series or anecdotal evidence. It is reassuring to note that only 0.2% of immunoglobulin has been used for indications where there is no reasonable evidence for its efficacy. However, in only half of these cases has the PCT approved the use of immunoglobulin as a case of exceptionality. A more thorough breakdown of these figures is given in this chapter.

Ascertainment to the database in the first year has been recognised as an issue. A number of Trusts have not entered any information into the database, including some significant volume users, and the infusion data are incomplete. Incomplete data compromise the accuracy of any conclusions that can be drawn. It is estimated from PASA that around 1000 kg of immunoglobulin (40% of total use) remains unaccounted for in the database. This is supported by the total use of immunoglobulin in GBS, where accurate incidence figures are available and there is strong evidence for the use of immunoglobulin treatment in patients with significant

and deteriorating disability. If the incidence of GBS is 1.2–1.5 per 100,000 population, then between 720 and 900 cases of GBS would be expected per year. Given that 60% of these require treatment with immunoglobulin,¹ the database would be expected to contain between 430 and 540 cases of GBS. With 260 GBS patients in the database, case ascertainment is between 48% and 60%. Clearly this can be improved in future years as the remaining Trusts provide data.

7.1 Immunoglobulin use for individual diagnoses

CIDP, GBS, MMNCB and MG account for 85% of the use of immunoglobulin in neurological indications, and for 36% of the total use of immunoglobulin in the database (Table 7.1). There is high-quality evidence for the use of immunoglobulin in CIDP, GBS and MMNCB, with no reasonable alternatives for most patients with MMNCB or with complicated and severe GBS.

Most patients with GBS receive a single dose of 2 g/kg over 5 days. Rarely, patients receive a second dose of immunoglobulin if there is a late deterioration or continued decline, but this practice is largely restricted to the very unwell in specialist centres. The average dose of immunoglobulin per patient in GBS is 144 g (i.e., just over 2 g/kg in a 70-kg average person), as would be expected.

A total of 151 patients with MG received approximately 250 g of immunoglobulin per patient or 1.8 full dose equivalent infusions per patient treated. Numbers of life-threatening MG relapses are relatively small. There is evidence of benefit from immunoglobulin in patients who are about to undergo surgery, especially thymectomy, and also in MG patients with acute severe deteriorations. There is no high-quality evidence to support continuous long-term use of immunoglobulin for MG, but it is clear from these data that a large number of MG patients are probably receiving relatively regular immunoglobulin. The numbers of patients are potentially large enough to support a well-designed RCT to answer the question of whether immunoglobulin is efficacious in MG in the longer term.

Diagnosis	n	Volume (g)	Average dosage (g/patient)
CIDP*	466	228,500	490
MMN	227	123,727	545
MG	151	37,770	250
GBS	260	37,481	144
Paraprotein-associated demyelinating neuropathy (IgM)	18	6604	367
Stiff person syndrome	13	6450	496
Polymyositis	24	4568	190
Paraprotein-associated demyelinating neuropathy (IgG or IgA)*	6	2086	348
Acute disseminated encephalomyelitis	11	1500	136
Lambert Eaton myasthenic syndrome	10	1308	131
Paraneoplastic disorders	7	1020	146
Multiple sclerosis	6	873	146
Vasculitic neuropathy	2	863	432
Bickerstaff's brain stem encephalitis	4	488	122
Inclusion body myositis	2	198	99
Acute idiopathic dysautonomia	1	180	180
Amyotrophic lateral sclerosis	1	72	72
Rasmussen syndrome	1	25	25
Intractable childhood epilepsy	1	20	20
Other (neurology)	90	35,198	391
Total	1301	488,929	

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.

*Red for short-term therapy but Blue for long-term therapy.

MMNCB and CIDP together account for most patients and the greatest use of immunoglobulin in all specialisms. Both are long-term conditions, and for most patients responding to immunoglobulin, recurrent infusions are required. It is interesting to note that, although MMNCB is reported to require lower doses of immunoglobulin than CIDP to maintain stability, MMNCB patients use on average 545 g of immunoglobulin per patient per year, compared with 490 g per patient per year in CIDP. MMNCB patients often require infusion more frequently than patients with CIDP, which may account for some of this difference. If one assumes that MMNCB patients require infusion every 4 weeks, then the dosage is about 0.6 g/kg per infusion for MMNCB compared with 1.1 g/kg per infusion for CIDP.

Table 7.1 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

Use of immunoglobulin in other neurological indications is relatively small. A diagnosis of 'other (neurology)' has been given for 7% of usage in neurology. At present it is not clear what the diagnoses in this group comprise. Further data mining and database development will elucidate these. The remaining 8% of patients (107 individuals) cover 15 diagnoses and account for only 5.4% of the neurological immunoglobulin use.

Short-term use also makes up a very minor part of immunoglobulin use (Table 7.2). Only 43,808 g of immunoglobulin (9% of total) were designated for short-term use. However, a weakness in the database means that it is not possible to distinguish short- and long-term treatment where the assigned Panel decision is Red. If GBS (monophasic), acute disseminated encephalomyelitis

and Bickerstaff's encephalitis (some use is wrongly classified as long term) are added, short-term use accounts for 15% of total immunoglobulin usage in 33% of patients. By deduction, patients designated as long-term users consume approximately 470 g immunoglobulin each per year, which equates to 6 g/kg, or approximately three 2-g/kg infusions per year.

7.2 Immunoglobulin use according to colour-coded prioritisation

For a diagnosis of CIDP, patients receive doses as a trial of therapy that may lead to long-term regular treatment. No patients with a diagnosis of CIDP should be

assigned a Panel decision of Grey. Surprising numbers of patients have been assigned a Panel decision of Red, indicating that without treatment, life-threatening complications would develop. In the Demand Management Programme, only short-term treatment is prioritised as Red. For MMNCB, a few patients have been assigned a Panel decision of Red; it would be interesting to look further at these to see how severe they are since MMNCB is rarely fatal. The cases assigned a Panel decision of Blue: short term are likely to be patients with 'probable disease' undergoing a trial of treatment. However, where long-term treatment *may* be indicated, patients should be trialled with a view to receiving long-term treatment, which should be assigned a Panel decision of Blue: long term.

Table 7.2 Volume of immunoglobulin used for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
CIDP*	34,016	170,798	11,367	2020	300			10,036	
MMN	2577	104,069	7721	225				9135	
MG	3400	17,561	12,045					4764	
GBS	30,738	80	1380					5284	
Paraprotein-associated demyelinating neuropathy (IgM)	770	5219	425					190	
Stiff person syndrome	1397	2795	1008		860			390	
Polymyositis	270	720	365	1648	915	180		470	
Paraprotein-associated demyelinating neuropathy (IgG or IgA)*	363	1723							
Acute disseminated encephalomyelitis				333	1018			150	
Lambert Eaton myasthenic syndrome		905	228					175	
Paraneoplastic disorders	120	125		250	525				
Multiple sclerosis					225		648		
Vasculitic neuropathy				665	198				
Bickerstaff's brain stem encephalitis				175	313				
Inclusion body myositis		163				35			
Acute idiopathic dysautonomia						180			
Amyotrophic lateral sclerosis						72			
Rasmussen syndrome								25	
Intractable childhood epilepsy								20	
Other (neurology)	903	15,855	1035	8296	4106	1190	25	3494	295

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading. *Red for short-term therapy but Blue for long-term therapy.

A small number of patients have been assigned a Panel decision of Red where Blue is more appropriate, for example, in stiff person syndrome and paraprotein-associated demyelinating neuropathy (IgM). It is interesting to note that two patients with polymyositis, one with a paraneoplastic disorder and two with IgA/IgG paraprotein-associated demyelinating neuropathy, were assigned a Panel decision of Red, implying that weakness was severe enough to warrant immediate treatment, as is known to occur sometimes.

Twelve patients with a variety of neurological conditions have been approved by Panels to receive immunoglobulin under exceptionality criteria. This is a small number of patients for whom, it is presumed, good evidence of exceptionality has been put forward.

Overall, the most striking findings from the Panel decisions assigned are the number of patients without a decision and the large number of CIDP patients with Red decisions (of which most should probably be Blue), but that Panels are clearly considering diagnoses and classifying them, to an extent, according to the Demand Management Programme. Some improvement in the database will be required to force entry to an appropriate category. For example, where a patient has a paraneoplastic syndrome, however severe it is, only a Grey decision is appropriate and as such the PCT would need to be contacted to seek approval before (preferably) or after immunoglobulin is given.

7.3 Immunoglobulin use in diagnoses with lack of evidence of efficacy ('Grey' and 'other' indications)

A total of 140 patients received immunoglobulin for 'Grey' or 'other' indications, those for which there is no RCT evidence, but there is evidence of benefit from

case reports and small case series. This still constitutes only 11% of the neurology patients in the database and 9% of the use by volume. 'Other' indications, still to be elucidated, constitute two-thirds of these. Polymyositis remains the biggest user in the identified Grey category, with 24 patients, half of whom are using immunoglobulin in the long term. Paraneoplasia covers a range of conditions associated with a range of antibodies, and this overlaps with the antibody mediated encephalitis cases. All are rare, and some very acute. Of the seven entries, in four the use is short term and in five the Panel decision is correctly assigned as Grey. The single 'Red' patient may well have been unwell enough to require urgent treatment but still should have been assigned a Panel decision of Grey. Volumes given indicate single doses for all patients. The single patient requiring immunoglobulin long term should also be assigned a Panel decision of Grey and immunoglobulin use approved by the PCT if response is demonstrated. The spread of Red, Blue and Grey assigned Panel decisions across the 'Grey' indications once again indicates either mistaken database entries or misunderstanding of the Demand Management Programme. Overall, usage of immunoglobulin in 'Grey' indications in neurology is proportionately small and covers a range of rare diagnoses.

7.4 Immunoglobulin use in diagnoses with evidence of a lack of efficacy ('Black' indications)

The identification of a group of 'Black' conditions where there is good evidence of a lack of efficacy for immunoglobulin was intended to restrict use in these conditions, unless exceptionality could be demonstrated. Only nine patients in the database have been prescribed immunoglobulin for 'Black' indications. It is reassuring

Table 7.3 Number of patients receiving immunoglobulin for diagnoses with lack of evidence of efficacy ('Grey' and 'other' indications)

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
Acute disseminated encephalomyelitis				2	8			1	
Acute idiopathic dysautonomia						1			
Bickerstaff's brain stem encephalitis				1	3				
Intractable childhood epilepsy								1	
Paraneoplastic disorders	1	1		1	4				
Polymyositis	2	2	2	10	5	1		2	
Vasculitic neuropathy				1	1				
Other (neurology)	7	20	4	14	23	6	1	13	2

Table 7.4 Number of patients receiving immunoglobulin for diagnoses with evidence of a lack of efficacy ('Black' indications)

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
Amyotrophic lateral sclerosis						1			
Inclusion body myositis		1				1			
Multiple sclerosis						2		4	

Table 7.5 Recorded use of alternatives prior to request for immunoglobulin in individual diagnoses

Diagnosis	Cyclophosphamide	Methotrexate	Corticosteroids	Rituximab	Ciclosporin	Other
Chronic inflammatory demyelinating polyradiculoneuropathy	7	26	132	5	6	38
MG	1	9	57		1	34
Other (Neurology)		1	31	2	1	4
Polymyositis	2	5	13		2	3
MMN	4	2	11	2	1	3
Lambert Eaton myasthenic syndrome		1	6			2
Stiff person syndrome			3	1		3
Acute disseminated encephalomyelitis			6			
GBS			4		1	1
Paraprotein-associated demyelinating neuropathy (IgM)	1		1	3		
Paraneoplastic disorders	1		2	1		
Intractable childhood epilepsy			1	1		1
Multiple sclerosis			3			
Paraprotein-associated demyelinating neuropathy (IgG or IgA)			2			1
Bickerstaff's brain stem encephalitis			2			
Rasmussen syndrome			1			1
Vasculitic neuropathy			1			1
Amyotrophic lateral sclerosis						1

that four of these have been approved through an exceptionality Panel, and only one patient, with inclusion body myositis, has been assigned a Panel decision of Blue. Four patients with multiple sclerosis still receive immunoglobulin without a Panel decision. The impact of this use is tiny and use is assumed to be short-term only on the basis that the total used is 1143 g or 0.2% of the annual neurology immunoglobulin usage, averaging only 1.8 g/kg per patient.

7.5 Recorded use of alternatives prior to request for immunoglobulin

Corticosteroids are the most frequently tried alternative prior to immunoglobulin use in any of the conditions for which immunoglobulin is prescribed. Only 28% of patients with CIDP had received a trial of steroids prior to immunoglobulin treatment. This is perhaps a small proportion, but probably reflects the reduced short- and

long-term side-effect profile of immunoglobulin over long-term high-dose corticosteroids. In CIDP, 6% of patients had been tried on methotrexate, but following the results of the RMC trial,² this number may fall to zero. The use of rituximab in CIDP (5 patients) is novel; a trial of rituximab as an immunoglobulin-sparing agent is being planned.

Interestingly, only 51 of 157 patients with MG had had a trial of steroids prior to immunoglobulin. Given the poor evidence base supporting treatment of MG with immunoglobulin, and good evidence that steroids are effective, this is surprising. A greater proportion of the patients had tried ‘other’ therapies, presumed to be cholinesterase inhibitors.

Other interesting points here are the use of steroids in 11 patients with MMNCB, which may cause this condition to worsen, and in four patients with GBS, which

would be discouraged as it may be harmful.³ These most likely represent data entry errors.

7.6 Recorded consideration of plasma exchange prior to request for immunoglobulin

Plasma exchange is not immunologically equivalent to immunoglobulin, but in some conditions is equally efficacious (e.g., in GBS and CIDP). In some conditions (MMNCB), it may worsen the illness; in others it may have no effect. Access to plasma exchange for neurological indications is patchy and unreliable.

The data are not particularly reliable because of the misinterpretation of the ‘Not applicable’ category

Table 7.6 Recorded consideration of plasma exchange prior to request for immunoglobulin

Diagnosis	Considered but not available	Considered but patient not suitable	Tried and failed	Not applicable	Not recorded
Acute disseminated encephalomyelitis	2	1	1	6	1
Acute idiopathic dysautonomia				1	
Amyotrophic lateral sclerosis				1	
Bickerstaff's brain stem encephalitis				4	
Chronic inflammatory demyelinating polyradiculoneuropathy	22	39	16	351	41
GBS	36	23	1	176	24
Inclusion body myositis				2	
Intractable childhood epilepsy	1				
Lambert Eaton myasthenic syndrome	3			7	
MMN	3	9	1	203	11
Multiple sclerosis		1		5	
MG	24	25	3	87	13
Other (Neurology)	7	9	7	58	9
Paraneoplastic disorders	1	2		4	
Paraprotein-associated demyelinating neuropathy (IgG or IgA)	1	3		2	
Paraprotein-associated demyelinating neuropathy (IgM)	1	3	1	12	1
Polymyositis	4			18	2
Rasmussen syndrome				1	
Stiff person syndrome	2	3		8	
Vasculitic neuropathy				2	

Data show number of treatment episodes where plasma exchange was considered.

by users. In some cases, such as MMNCB, plasma exchange is not efficacious and may be harmful and hence 'not applicable' or 'not suitable' (212 of 227 cases) is appropriate. However, 351 of 466 patients with CIDP were in the 'Not applicable' category. Before these data can really be used for meaningful planning purposes, the database and immunoglobulin submission form headings need to be clarified to classify entries unambiguously.

7.7 Assessment of outcomes

The assessment of the outcome of immunological treatment in neurological diseases is difficult to address. Some conditions, such as the neuromuscular diseases CIDP and MG, have clearly measurable validated outcomes; these cover the areas of impairment, disability and handicap.

The recent 131st European Neuromuscular Centre International Workshop outlined easily measurable outcomes for triallists studying CIDP.⁴ For CIDP, these are three of:

- MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70)
- Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score
- Overall Neuropathy Limitations Scale (ONLS)
- 10-m walk.

MMNCB is more difficult to assess due to its patchy nature, which means that it is not so consistent across individuals. The ENMC recommended that outcomes should be two of:

- Power score from 10 predefined pairs of muscles including six most affected muscles neurophysiologically
- ONLS
- 10-m walk.

Outcome measures have been recorded for most neuromuscular disorders. In many cases, a 9-hole peg test or grip strength has been recorded. This is possible for large centres with access to assessment tools, but these tools are not available in every centre and so the scores that require no special equipment and are valid, reliable and easy to perform are recommended.

The scores above also apply to other neuropathies, but are less relevant to myopathy and not relevant to other non-neuromuscular disease. For instance, voltage gated potassium channel associated limbic

encephalitis may present with memory difficulty, personality change, seizures and/or sleep disturbance, and stiff person syndrome presents with stiffness for which there are no reliable impairment scores available. These are more difficult to measure and quantify, and also to prospectively define. Appropriate outcome measures should be identified on the basis of the impairments and disabilities of individual patients and a range of appropriate scores generated that are measured before and after therapy.

If trials are considered in the future, a consensus group of outcome measures should be developed such that outcomes can be compared across individuals.

7.8 Conclusions

- Immunoglobulin prescribed for neurological indications is responsible for 40% of immunoglobulin use in England. In 2008–9, use has stabilised. Most (85%) neurological use is for the four most common indications, three of which are supported by good RCT evidence for effectiveness both in the short and long term, where applicable.
- The use of immunoglobulin for 'Grey' indications is minimal, and most is supported by Panel decisions or has been referred appropriately to PCTs for consideration of funding.
- The use of immunoglobulin for indications prioritised by the Demand Management Programme as Black is minuscule and will hopefully decrease, apart from exceptionality cases. There is no evidence that immunoglobulin is being used widely for proliferating indications unsupported by an evidence base.
- Short-term use (probably covering both monophasic disease and 'trials' of treatment) accounts for a small proportion of immunoglobulin use but one-third of the patients on the database. Patients using immunoglobulin long term have the equivalent of only three infusions per year each, which is fewer than expected.
- For MG, there are probably enough patients to support an RCT of immunoglobulin use. Unfortunately, for other rarer diagnoses the numbers of patients are likely to be too few and hence formal structured N=1 trials might be indicated.
- A number of database issues are clear from the entries in the first year. Full entry of all immunoglobulin use in England has not been achieved and, using the epidemiology of GBS, it would appear that between 48% and 60% entry has been achieved, which correlates with the PASA estimates.

- The Demand Management Programme colour-coded prioritisation is the cause of some confusion; the database should be modified to force entries into only the applicable colour-coded groups.
- Recording the use of lower dose or higher dose per day and frequency in repeat users would be valuable.
- Overall, the data demonstrate appropriate and controlled use of immunoglobulin for a wide range of neurological conditions and evidence-based use for the greater part. This reflects positively on the neurologists in the UK, who have signed up to the demand management process and continue to treat their patients on the best evidence available.

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CHAPTER 8

Dermatology

Daniel Creamer

The usage of immunoglobulin for dermatological conditions in England is modest. Figures from the National Immunoglobulin Database indicate small patient numbers, with seven cases of toxic epidermal necrolysis (TEN) and two of Stevens Johnson syndrome (SJS), six of immunobullous disorders, three of urticaria and two of pyoderma gangrenosum (PG), plus 15 cases with a diagnosis of 'other (dermatology)'. The low administration of immunoglobulin in dermatology may reflect not only the lack of good-quality evidence for its use in these dermatological conditions, but also the rarity of the indicated skin diseases. In addition, low patient numbers may indicate suboptimal data collection.

8.1 Immunoglobulin use for individual diagnoses

SJS and TEN are terms used to describe a life-threatening, muco-cutaneous drug hypersensitivity syndrome characterised by blistering and epidermal sloughing. SJS lies at the milder end of the clinical spectrum, TEN at the severe end. Mortality is related to the extent of skin surface area involved. Outcome studies of SJS/TEN indicate that 20–30% of patients do not survive. The disease

is characterised by extensive epithelial keratinocyte apoptosis mediated in part by the Fas-Fas ligand pathway. Evidence for a therapeutic benefit of immunoglobulin in SJS/TEN is derived from data demonstrating that high concentrations of human immunoglobulin are capable of inhibiting Fas-Fas ligand interaction and keratinocyte apoptosis through anti-Fas activity.¹

There are no controlled studies of immunoglobulin in SJS/TEN, but a multicentre retrospective analysis of 48 SJS/TEN cases treated with immunoglobulin demonstrated significantly higher survival than studies in which only supportive care had been used.² However, a range of immunoglobulin doses were used (0.65–5.8 g/kg, mean 2.7 g/kg), infused over a varied number of days (1–5 days, mean 4 days). The authors stated that patients who responded to immunoglobulin received treatment earlier and at higher doses. A treatment regime of 3 g/kg over 3 consecutive days was recommended. It is on the basis of this study and other smaller case series that immunoglobulin is used in TEN. However, a study from Roujeau's group, which has a long record of high-calibre research into SJS/TEN, was unable to identify a survival advantage in a series of 34 patients treated with 2 g/kg immunoglobulin infused over 2 days.³

Diagnosis	n	Volume (g)	Average dosage (g/patient)
Immunobullous diseases	6	2330	388
Toxic epidermal necrolysis*	7	1124	160
Stevens Johnson syndrome*	2	188	94
Urticaria	3	475	158
Pyoderma gangrenosum	2	450	225
Other (dermatology)	15	7283	486
Total	35	11,850	

Table 8.1 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.

*Red for short-term therapy but Blue for long-term therapy.

There are currently no evidence-based guidelines on the management of SJS/TEN, although the British Association of Dermatologists (BAD) has recently commissioned a document on this subject. Despite the conflicting literature, UK dermatologists (and other clinicians caring for SJS/TEN patients, such as burns plastic surgeons) routinely prescribe immunoglobulin in SJS/TEN cases where there is extensive epidermal loss. The incidence of SJS/TEN has been estimated at 1–2 cases/million population/year. Therefore, approximately 60–120 cases of SJS/TEN would be expected per year. Assuming that 50% of these have a degree of epidermal loss to warrant immunoglobulin (>10% of body surface area), then the database would be expected to contain between 30 and 60 cases (9 cases registered). The discrepancy between cases identified and total SJS/TEN numbers may be improved in future years as data collection becomes more complete. The average immunoglobulin dose per patient on the database, 160 g in TEN and 94 g in SJS, is probably slightly less than the recommended 3 g/kg. In the future, demand for immunoglobulin in SJS/TEN may be influenced by the publication of the BAD guidelines and by further studies that clarify the place of immunoglobulin, and its optimum dosing regimen, in the management of this disease.

There is better-quality evidence for the use of immunoglobulin in immunobullous disorders, especially pemphigus. Systemic corticosteroids, usually given at high dose and for prolonged periods, are the mainstay of treatment in the immunobullous diseases. Consequently, steroid-induced side-effects are common and the use of steroid-sparing adjunctive therapy is usually necessary. High-dose immunoglobulin has been found to be effective in controlling blistering through a range of pathways including the blockade of skin-directed auto-antibodies, which mediate these disorders. A review of all case reports and case series of immunoglobulin in

immunobullous diseases indicated that immunoglobulin was effective in over 80% of patients.⁴ More recently, a randomised, placebo-controlled, double-blind trial in 61 pemphigus patients given a single cycle of immunoglobulin administered over 5 days demonstrated a significantly positive disease response.⁵ Other studies have demonstrated that immunoglobulin can lower circulating levels of pathogenic antibodies in pemphigus. Despite the encouraging evidence for its role in pemphigus, only six patients with immunobullous disorders have been registered in the database. The best-quality evidence for the use of immunoglobulin is in pemphigus, so it would be interesting to see whether this bias is reflected in the series. Of the six patients, specific details of diagnosis are available for only one patient, who had mucous membrane pemphigoid; in addition, one patient had concomitant SJS/TEN.

8.2 Immunoglobulin use according to colour-coded prioritisation

The assigned Panel decisions for about half of the patients (18, 51%) were in keeping with the Demand Management Programme. However, one patient with immunobullous disease was assigned a Panel decision of Red, when the Demand Management Programme prioritises immunobullous disease as Blue. In addition, eight patients with a listed diagnosis of 'other (dermatology)', which is prioritised as Grey by the Demand Management Programme, were also assigned a Panel decision of Red. For four of these patients, no further information was available. Of the other four patients, three had SJS, one with concomitant brain carcinoma, and the fourth had TEN secondary to ibuprofen. In all of these, an assigned Panel decision of Red would be appropriate.

Table 8.2 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
Immunobullous diseases	1	3						2	
Toxic epidermal necrolysis*	6					1			
Stevens Johnson syndrome*	1							1	
Pyoderma gangrenosum				1	1	1			
Urticaria				1	1	1			
Other (Dermatology)	8		2	2	1			2	

Prioritisation in the Demand Management Programme is shown by shading. *Red for short-term therapy but Blue for long-term therapy.

8.3 Immunoglobulin use in diagnoses with lack of evidence of efficacy ('Grey' and 'other' indications)

In PG, single case studies and case series have reported a positive outcome with immunoglobulin, but there are no controlled trials. In the largest series of 10 cases, patients were treated with 2 g/kg given over 3 days each month.⁶ Six patients had complete and sustained healing of PG with repeated cycles of treatment. The database has identified only two cases of PG treated with immunoglobulin, which reflects the Grey prioritisation for this disorder and indicates a lack of good-quality evidence. The average immunoglobulin dose per patient on the database was 225 g, which is probably appropriate given the suggested dosing regimens.

Chronic urticaria is a common dermatological problem that can usually be controlled with H₁ antihistamines. However, rarer subtypes including urticarial vasculitis and the physical urticarias often require an alternative therapeutic approach. For several years, immunoglobulin has been used in cases of difficult chronic urticaria resistant to other treatments. There are single

case studies and case series reporting a positive outcome in the management of urticarial vasculitis and solar urticaria, in particular. Nonetheless, the absence of controlled studies means that the quality of evidence for immunoglobulin efficacy in urticaria is poor. The database contains three cases of urticaria, but no details are recorded of subtype. Since chronic urticaria is relatively common, the small number of cases treated with immunoglobulin suggests that this therapeutic approach is not commonly adopted. The use of immunoglobulin in chronic urticaria in the future is likely to be limited to isolated cases, particularly in the rarer subtypes of physical urticaria or where urticaria is a manifestation of cutaneous vasculitis.

8.4 Recorded use of alternatives prior to request for immunoglobulin

Systemic corticosteroids are the primary alternative to immunoglobulin in most of the immunoglobulin-treated disorders with the exception of urticaria. There is good evidence for the use of ciclosporin in controlling

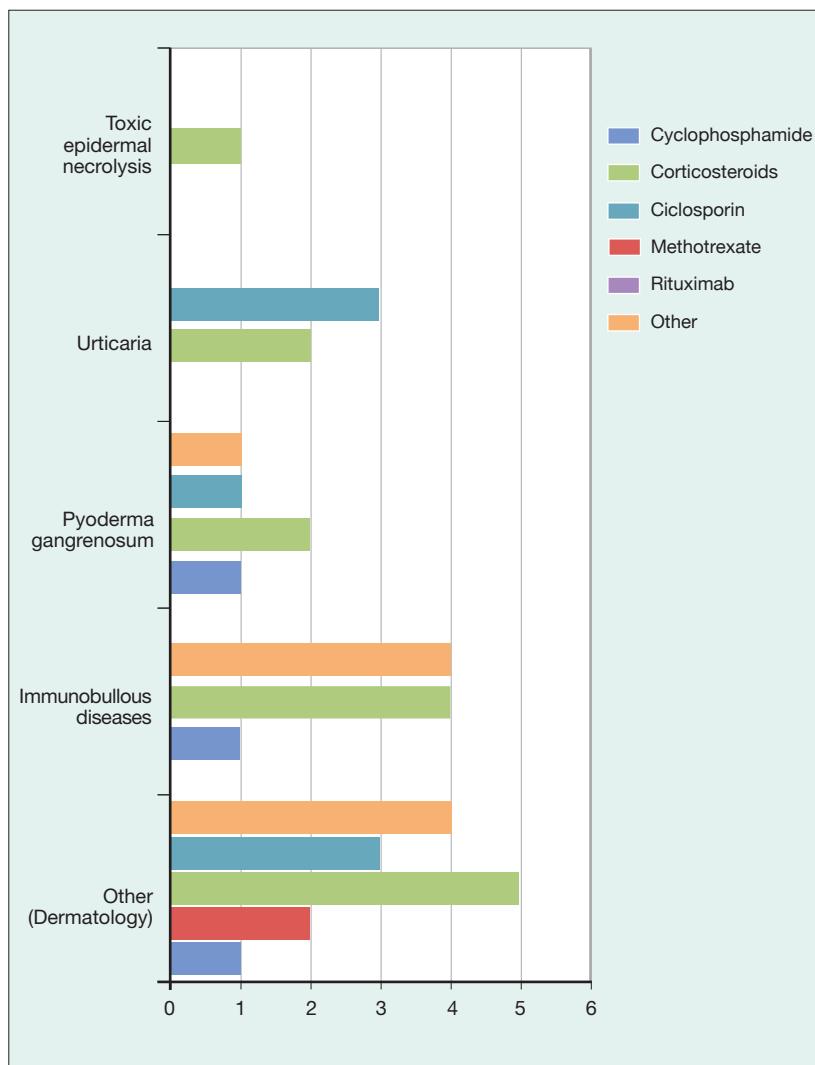


Figure 8.4 Recorded use of alternatives prior to request for immunoglobulin in individual diagnoses.

difficult urticaria, whereas oral glucocorticoids are, in general, not recommended. In SJS/TEN, systemic corticosteroids are effective in early disease with limited involvement (SJS), but they worsen mortality in cases with widespread epidermal loss (TEN).

In the immunobullous diseases, corticosteroids and ‘other’ therapies are used equally; the other therapies may include B-cell depletion therapy in the form of rituximab. Recently, rituximab has gained recognition as a powerful and effective agent in the management of recalcitrant cases of immunobullous disorders. Consequently, the numbers of patients with autoimmune blistering disease receiving immunoglobulin may diminish with time as more rituximab is used.

Corticosteroid is the first-line treatment for PG, which is reflected in the data. The anti-tumour necrosis factor (TNF) agent infliximab is effective in PG, and the evidence for its efficacy is greater than that for immunoglobulin. Despite the more prominent side-effect profile of anti-TNF therapy, the therapeutic advantage of infliximab may limit further demand for immunoglobulin in PG.

8.5 Recorded consideration of plasma exchange prior to request for immunoglobulin

Among the dermatological conditions, plasma exchange is only a recommended alternative for immunobullous diseases. However, it was only considered for one patient, who was deemed an unsuitable candidate. It was considered in one patient with PG, although it is not a recommended alternative; again, the patient was not deemed suitable.

8.6 Conclusions

- Immunoglobulin use in dermatological conditions in England is modest, reflecting both the lack of clinical evidence and the rarity of the indicated skin diseases.
- In total, 35 patients were treated with 12 kg of immunoglobulin.
- The most common diagnosis was TEN and the biggest volume user was immunobullous disease.
- Only around half of the decisions assigned by the Panels are in keeping with the prioritisation of the Demand Management Programme.
- One-third of patients with dermatological diseases requiring immunoglobulin had a recorded diagnosis of ‘other’.

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CHAPTER
9

Rheumatology

Patrick Gordon

As a specialism, rheumatology is a minor user of immunoglobulin, accounting for 227 patients (4.4%) and only 2.5% of the volume used (28,219 g).

Kawasaki disease and dermatomyositis (adult and juvenile) together accounted for 148 (65%) of rheumatology patients treated with immunoglobulin. These are the only two rheumatological conditions prioritised by the Demand Management Programme as Red and as such are 'considered the highest priority because of a risk to life without treatment'. In Kawasaki disease, immunoglobulin is recommended routinely, whereas in dermatomyositis it is recommended for selected cases only. Thus, despite its rarity, Kawasaki disease was the most common indication for immunoglobulin in rheumatology, accounting for 101 patients (44.5%).

The other main indications for immunoglobulin were SLE (including juvenile SLE and SLE with secondary immunocytopenias) and vasculitides other than Kawasaki disease (systemic vasculitides and ANCA disorders and other systemic vasculitides), accounting for 44 patients (19%). SLE and ANCA-associated vasculitis are prioritised by the Demand Management Programme as Grey, as the evidence for efficacy is essentially confined to case reports and case series. Catastrophic anti-phospholipid syndrome and juvenile idiopathic arthritis, two other indications prioritised as Grey, accounted for a further nine patients. Two patients received immunoglobulin for rheumatoid arthritis, a 'Black' indication where there is good evidence for lack of efficacy. Since rheumatoid arthritis occurs in 1% of the population, this represents a negligible proportion of patients with the disease.

In 24 patients with a listed diagnosis of 'other (rheumatology)', the specific diagnosis was not available. In addition, not all Trusts have entered data into the database and approximately 9% of all patients had no diagnosis recorded. Therefore, the data presented in this chapter are incomplete and should be interpreted with caution.

9.1 Immunoglobulin use for individual diagnoses

Kawasaki disease is a rare condition with an estimated annual incidence of 8.4/100,000 in the under fives from 1998 to 2003 in the UK.¹ However, data from RCTs and meta-analyses have demonstrated a marked reduction in the formation of cardiac aneurysms with immunoglobulin therapy. Therefore, immunoglobulin is indicated as first-line therapy in all patients presenting acutely. The standard dose is 2 g/kg given once only, except in refractory disease where further doses may be required; the average use per patient treated on the database was 36 g/patient, broadly in line with this dose, given the age group.

In total 101 Kawasaki patients were treated, accounting for 44.5% of the rheumatology cohort. Based on the Office of National Statistics (ONS) population estimates, the UK population of under fives was approximately 1,895,100 in 2008. Thus, even if all the cases treated with immunoglobulin were assumed to be under 5 years of age, this would give an incidence of only 5.3/100,000 in the UK, below the estimated incidence of 8.4/100,000. This may be explained by the fact that ascertainment to the database has been a problem in this first year, with a substantial proportion of the total immunoglobulin usage unaccounted for. In addition, some patients presenting late may not have received immunoglobulin therapy.

Dermatomyositis was the second most frequent rheumatological indication, with 44 adult cases and three juvenile cases accounting for 21% of rheumatology patients treated. The use of immunoglobulin in dermatomyositis is essentially based on one small RCT that demonstrated benefit in manual muscle strength at 3 months.² Nonetheless, this remains the only RCT that has shown benefit for any immunosuppressive or immunomodulatory agent in dermatomyositis or the other idiopathic inflammatory myopathies.

Diagnosis	n	Volume (g)	Average dosage (g/patient)
Dermatomyositis*	44	9919	225
Kawasaki disease*	101	3656	36
Other systemic vasculitides	5	3097	619
Systemic lupus erythematosus	21	2721	130
Systemic vasculitides and ANCA disorders	11	1668	152
Systemic juvenile idiopathic arthritis	6	1293	216
Juvenile dermatomyositis*	3	580	193
Catastrophic antiphospholipid syndrome	3	578	193
Systemic lupus erythematosus with secondary immunocytopenias	5	480	96
Rheumatoid arthritis	2	389	195
Juvenile systemic lupus erythematosus	2	80	40
Other (Rheumatology)	24	3761	157
Total	227	28,219	

Table 9.1 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.

*Red for short-term therapy but Blue for long-term therapy.

Table 9.2 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
Dermatomyositis*	24	13	1					5	1
Kawasaki disease*	93		1					7	
Systemic lupus erythematosus			1	5	7			7	1
Systemic vasculitides and ANCA disorders	1			2	7				
Systemic juvenile idiopathic arthritis				4				1	1
Other systemic vasculitides				5					
Systemic lupus erythematosus with secondary immunocytopenias	2				1			2	
Catastrophic antiphospholipid syndrome					1			2	
Juvenile systemic lupus erythematosus				2					
Rheumatoid arthritis	1			1					
Juvenile dermatomyositis*	1	2							
Other (Rheumatology)	1		1	6	4	1		9	2

Prioritisation in the Demand Management Programme is shown by shading. *Red for short-term therapy but Blue for long-term therapy.

In addition to the 47 dermatomyositis cases, 24 cases of polymyositis and two of inclusion body myositis (despite the latter not being an approved indication) were also treated in this period (see Chapter 7). Thus, there were 73 cases of idiopathic inflammatory myopathy, of which 68 patients had adult polymyositis or dermatomyositis. The prevalence of polymyositis and dermatomyositis is estimated at 20/100,000 population.³ Based on ONS population estimates, the UK population was approximately 61,383,200 in mid 2008, giving a UK population of approximately 12,280 patients with polymyositis and dermatomyositis. Based on this estimation, less than 1% of the polymyositis and dermatomyositis population received immunoglobulin.

Most of the remaining patients were treated for SLE (28 patients), vasculitis (16 patients) or juvenile idiopathic arthritis (6 patients), which are 'Grey' indications. Considering the prevalence of these conditions, it is clear that immunoglobulin is being used very rarely and not as part of routine care.

Catastrophic antiphospholipid syndrome is a rare condition with a high mortality for which there is unlikely ever to be an RCT. However, a registry-based study suggested that there may be benefit from plasma exchange or immunoglobulin in combination with anticoagulation and supportive therapy.⁴ Only three patients received immunoglobulin for this indication.

Two patients received immunoglobulin for rheumatoid arthritis, which is a 'Black' indication where use should be restricted unless exceptionality can be demonstrated. In view of the fact that approximately 1% of the UK population has rheumatoid arthritis and only two patients were treated with immunoglobulin, it would seem likely they were exceptional cases. However, they were not treated under exceptionality criteria.

9.2 Immunoglobulin use according to colour-coded prioritisation

In 123 rheumatology patients (54%), local Panels assigned a decision of Red, indicating 'a risk to life without treatment'. Of these patients, 118 had either dermatomyositis or Kawasaki disease, but another five had other indications that according to the Demand Management Programme should be assigned a different decision. In a significant number of cases (38, 17%), the Panel's decision was either awaited or not recorded.

Of the 64 patients assigned a Panel decision of Grey or Blue, 40 (63%) were on long-term therapy. These

were spread over a broad range of indications, although appropriately all the patients on Blue long-term therapy had dermatomyositis. However, since the main 'Red' indication, Kawasaki disease, is a short-term indication, it is likely that most rheumatology patients received short-term therapy.

In two patients, the diagnosis given was rheumatoid arthritis, which should be a 'Black' indication according to the Demand Management Programme. In one patient, the assigned Panel decision was Red and in the second patient it was Grey: long term. Neither patient had any additional diagnosis according to the data available, but the patient assigned a Panel decision of Red was receiving ongoing treatment under an immunologist and the other patient was also receiving ongoing treatment. Without further information it is difficult to comment on these cases; they may have had exceptional reasons for requiring immunoglobulin therapy. These two patients only received 389 g of immunoglobulin.

9.3 Recorded use of alternatives prior to request for immunoglobulin

As might be expected, a broad range of alternative immunosuppressive agents had been tried prior to immunoglobulin therapy in patients with SLE and ANCA-associated systemic vasculitis. Interestingly, only a minority of patients with SLE (4, 14%) or ANCA-associated vasculitis (4, 36%) had had prior therapy with cyclophosphamide. This might suggest that the use of immunoglobulin was not directed uniquely at patients with the most severe disease. However, this cannot be assumed from the data and the reason for choosing immunoglobulin in these cases is not clear. Five patients with SLE had immunocytopenias and therefore had additional indications for immunoglobulin. Notably, other indications such GBS are also recognised as manifestations of SLE. Another important situation where immunoglobulin might be attractive is in patients with severe active disease and a suspected or confirmed concomitant infection.

With the exception of one patient who had had prior steroid therapy, immunoglobulin was, appropriately, the first immunotherapy agent used in all patients with Kawasaki disease. The use of prednisolone as a prior alternative was much lower than might be expected for many of the conditions, but this may be due to a lack of reporting rather than a true reflection of its use.

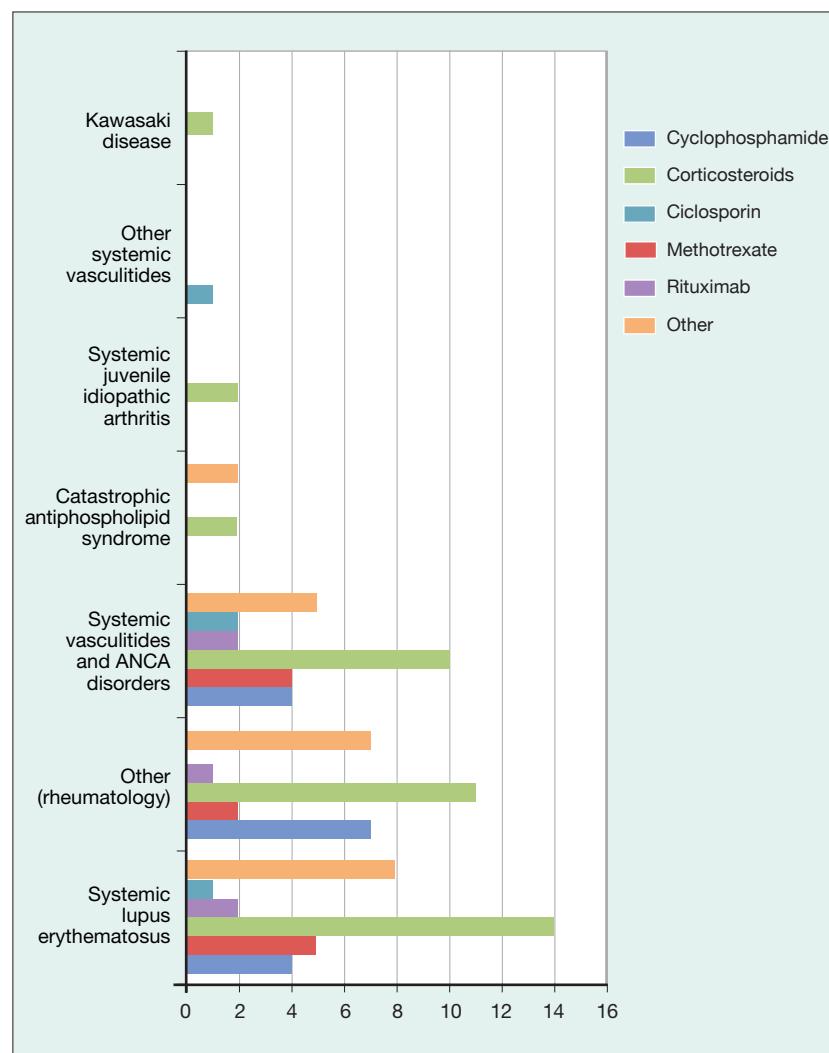


Figure 9.3 Recorded use of alternatives prior to request for immunoglobulin in individual diagnoses.

9.4 Conclusions

- The use of immunoglobulin is minimal in rheumatology, accounting for only 4.4% of recipients in England and an even smaller proportion of the volume used (2.5%).
- Kawasaki disease was the most frequent indication, accounting for 101 patients (44.5%), followed by dermatomyositis with 44 adult cases and three juvenile cases (21%).
- Considering that immunoglobulin is the only immunosuppressive or immunomodulatory therapy that has been shown by a RCT to provide benefit in dermatomyositis, it is surprising to find that less than 1% of patients with this condition received it over the year. Similarly, a very small number of patients with vasculitis and SLE received immunoglobulin.
- Further data as to the particular clinical situations within these diseases that induce clinicians to use immunoglobulin would help to better define its present role and guide future research.

- The use of immunoglobulin therapy was generally appropriate in rheumatology based on the data available.

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CHAPTER 10

Infectious diseases

Shiranee Sriskandan

The 1-year data extracted for this report confirm that infectious disorders account for a small proportion of immunoglobulin use in England. In total, 184 patients (3.5%) consumed a total of 16,018 g (1.4%). Unfortunately, a specific diagnosis was not given for about one-quarter of the recorded use. It is important to understand the indications for which immunoglobulin is prescribed, even if the diagnosis is not confirmed when immunoglobulin is administered. Further analysis of these cases is presented in this chapter.

As expected, the largest volume of immunoglobulin was used in severe invasive group A streptococcal (GAS) disease, although the largest number of patients (67) were treated for severe or recurrent *Clostridium difficile* colitis. Most patients (accounting for about half the volume used) have been treated correctly within the Blue: short term category, as prioritised by the Demand Management Programme. However, there is significant use in cases for which the assigned Panel decision is inconsistent with the Demand Management Programme, including usage assigned a Panel decision of Red.

No use was entered for post exposure prophylaxis for viral infection, which is prioritised by the Demand

Management Programme as Grey, but further investigation of the cases that lacked a diagnosis revealed two cases of use for measles prophylaxis; one was a pregnant woman exposed to measles and the other was a 5-year-old girl with no complications listed. Three cases received immunoglobulin for indications prioritised as Black, although these cases were not treated under the correct process of applying for exceptional use through the PCT. Taken together, these findings suggest that inappropriate prescribing of immunoglobulin in infectious diseases is minimal. The most commonly used alternatives to immunoglobulin were as expected and included antimicrobials, mostly antibiotics.

10.1 Immunoglobulin use for individual diagnoses

The largest volume of immunoglobulin (4451 g, 29%) was used in severe invasive GAS disease. The mean dose was 2 g/kg, assuming an average 70-kg patient. If most patients are adults, it appears that the correct dose is being used.

Table 10.1 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

Diagnosis	n	Volume (g)	Average dosage (g/patient)
Severe invasive group A streptococcal disease	31	4451	144
Necrotising (PVL-associated) staphylococcal sepsis	20	2673	134
Severe or recurrent <i>Clostridium difficile</i> colitis	67	2297	34
Staphylococcal toxic shock syndrome	11	1388	126
Toxin-related infection in paediatric intensive care	19	719	38
Sepsis in the intensive care unit not related to specific toxins or <i>Clostridium difficile</i>	3	384	128
Neonatal sepsis (prevention or treatment)	2	10	5
Other (infectious diseases)	31	4096	132
Total	184	16,018	

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.

The high mortality associated with this condition, late presentation and frequent deterioration despite conventional therapy might be expected to create a high demand for adjunctive therapy. However, the 31 patients listed in the database represent only a small percentage (2–3%) of reported invasive GAS disease cases. This may be because immunoglobulin is reserved as salvage therapy for the sickest patients, or because clinicians are unconvinced (or unaware) of a role for immunoglobulin in this setting. Surveillance studies show that the annual incidence of invasive GAS disease is between 1200 and 1700 cases per year;¹ incidence increased at the start of 2009 for reasons that are currently unclear.²

A diagnosis of 'other (infectious diseases)' was recorded for 31 patients, using more than 4 kg immunoglobulin. When the individual database records for these patients were examined in detail, only seven patients had no diagnosis. Eight of the remaining 22 patients were apparently mis-assigned and the patients had immunological or haematological conditions for which immunoglobulin is deemed appropriate therapy. Two additional patients had received immunoglobulin as measles prophylaxis. Among the remaining 12 patients, diagnoses included secondary antibody deficiency in a patient with chronic lung disease, autoimmune neutropenia, previous lung transplant/heart disease and parvovirus infection, long-standing *C. difficile* diarrhoea, toxin-associated staphylococcal or streptococcal infection (3 patients), allergic bronchopulmonary aspergillosis, herpes zoster, HIV chronic norovirus, enteroviral infection in a preterm neonate and ataxia telangiectasia.

The largest number of patients with a single diagnosis is 67 for severe or recurrent *C. difficile* colitis. There are 30,000–40,000 cases of *C. difficile* infection per year, of

which 2–5% are expected to be severe. If the figures are adjusted for the fact that the database has captured only 40–60% of immunoglobulin use, 0.3% of patients with *C. difficile* infection are receiving immunoglobulin. This suggests that clinicians are managing severe *C. difficile* infection with alternative strategies as outlined by existing DH/HPA guidelines. Where alternative strategies do not control severe or recurrent disease, the HPA suggests an immunoglobulin dose of 400 mg/kg, repeated once if necessary.³ Clinicians appear to be following this recommendation, as the mean dose is 490 mg/kg (appropriate for a 70-kg patient). With rates of *C. difficile* falling substantially, we may expect to see a reduced number of patients receiving immunoglobulin in the coming year.

Within the Clinical Guidelines, *C. difficile* infection was treated as a single condition, although immunoglobulin is suggested for both severe and recurrent infections that are refractory to standard treatments. It would be interesting to understand usage for the two indications separately; individual records only allow identification of three patients with recurrent infection and five with severe disease.

10.2 Immunoglobulin use according to colour-coded prioritisation

For all infectious diseases where immunoglobulin use is recommended in the Demand Management Programme, only short-term treatment is appropriate. It was envisaged that immunoglobulin would be used in critically ill patients, but nevertheless, no condition was prioritised as Red, as in almost all cases other therapies would be used before immunoglobulin. Immunoglobulin use was mostly assigned a Panel decision of Blue: short term.

Table 10.2 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
Severe invasive group A streptococcal disease	3		23		1			4	
Necrotising (PVL-associated) staphylococcal sepsis	2	1	13					4	
Severe or recurrent <i>Clostridium difficile</i> colitis	4	2	51		1			9	
Staphylococcal toxic shock syndrome			7		1			3	
Toxin-related infection in paediatric intensive care	4	1	11					1	
Sepsis in the intensive care unit not related to specific toxins or <i>Clostridium difficile</i>			3						
Neonatal sepsis (prevention or treatment)							2		
Other (infectious diseases)	11	2	6		6	1	1	4	

Prioritisation in the Demand Management Programme is shown by shading.

In severe invasive GAS disease, three patients were assigned a Panel decision of Red. Doses were higher in these patients (190 g/patient) than in patients assigned a Panel decision of Blue (150 g/patient). In addition, one patient was given short-term treatment with an assigned Panel decision of Grey.

In total, 24 patients were assigned a Panel decision of Red. Seven patients had additional immunological or haematological conditions where immunoglobulin is deemed appropriate treatment with prioritisation of Red. The remaining patients had pancytopenia from non-Hodgkin's lymphoma, toxin-related severe staphylococcal or streptococcal disease ($n=11$) or ataxia telangiectasia; there was no information on the remaining three patients. The assignment of a Red panel decision may have been due to the way that the local Panel interpreted the Clinical Guidelines, or because the Panel disagreed with the Blue prioritisation.

No use of immunoglobulin was assigned a Panel decision of Grey, but two cases of measles prophylaxis (prioritised as Grey by the Demand Management Programme) were recorded under a diagnosis of 'other (infectious diseases)'. More than 2200 g was used in 11 patients with no specific diagnosis and an assigned Panel decision of Red. Although this may have been because the condition was deemed to be life threatening, all conditions not listed in the Clinical Guidelines must be assigned a Panel decision of Grey, even if the condition is life threatening and the Panel approve immediate use. Some improvement in the database will be required to force entry into the relevant category. It will be important to further understand the conditions for which immunoglobulin is being used and the way that local Panels are interpreting the Demand Management Programme.

Only three patients received approval for use of immunoglobulin in indications prioritised as Black, although these were assigned a Panel decision of Blue: long term. The impact of this use is small (384 g, 2.4% of use in infectious diseases), but it is still important that the correct colour coding is used to allow accurate tracking of use. Two patients received treatment despite rejection of the request.

10.3 Recorded use of alternatives prior to request for immunoglobulin

The alternative therapies listed in the database (cyclophosphamide, methotrexate, corticosteroids, rituximab and ciclosporin) are not appropriate or relevant alternatives in patients with infectious diseases, where the aim is not immunosuppression but antibody support. It appears likely that all patients will have received antibiotics, although the information may be incomplete. No patients in this specialism received methotrexate or rituximab. Immunosuppressants, where used in two patients, were administered for pre-existing non-infectious diagnoses (ciclosporin for autoimmune neutropenia and

corticosteroids for allergic bronchopulmonary aspergillosis). Use of antibiotics was recorded for 48 patients, of activated protein C for two patients and of surgical debridement for three patients.

10.4 Recorded consideration of plasma exchange prior to request for immunoglobulin

Plasma exchange is not a suitable alternative treatment for any of these infectious diseases. However, it was tried in two patients, one with staphylococcal toxic shock syndrome and one with toxin-related infection in paediatric intensive care. It was also considered for two patients with necrotising (PVL-associated) staphylococcal sepsis and one with severe or recurrent *C. difficile* colitis, but was not available.

10.5 Conclusions

- Immunoglobulin prescribed for infectious diseases is responsible for 1.4% of the total used in England, with most use in severe invasive GAS disease, and the largest number of patients treated for severe or recurrent *C. difficile* colitis.
- There is little use outside the recommendations of the Demand Management Programme.
- About half of the volume has been used according to the Demand Management Programme prioritisation, but the use of the diagnosis of 'other' in infectious diseases has been widespread and inaccurate, compromising the quality of the data.
- The assignment of a Panel decision of Red or long-term use is a concern and highlights that in this first year there are several database entry issues. In particular, the meaning of the colour-coded Demand Management Programme indications appears to be causing some confusion; the database should be modified to force entries into only the applicable colour-coded groups.

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Transplantation

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The National Immunoglobulin Database reveals that transplantation is an appropriately low user of immunoglobulin overall. The 161 patients represent approximately 3% of the total, while the amount of immunoglobulin used is about 2.3% of global reported usage. CMV-induced pneumonitis is the only condition in this section prioritised as Red by the Demand Management Programme, so it is of concern that only two patients received immunoglobulin for this

indication. Treatment of acute antibody-mediated rejection following solid organ transplantation and antibody incompatible transplantation, the conditions prioritised as Grey, along with unspecified ‘other (transplantation)’ conditions almost equally split the remaining 159 patients. Hence, the data of reported immunoglobulin use in transplantation shows that it is largely for conditions with a limited evidence base and for unknown indications.

Diagnosis	n	Volume (g)	Average dosage (g/patient)
Ab-mediated rejection (solid organ)	61	11,838	194
Ab-incompatible transplantation	25	3885	155
CMV-induced pneumonitis following transplantation	2	90	45
Other (transplantation)	73	12,643	173
Total	161	28,455	

Table 11.1.1 Immunoglobulin use for individual diagnoses: numbers of patients, volume of immunoglobulin and calculated average dose per patient

The infusion data recorded in the database are incomplete; these data should be interpreted with caution. Prioritisation in the Demand Management Programme is shown by shading.

Table 11.1.2 Number of patients receiving immunoglobulin for individual diagnoses under Panel-assigned prioritisation

Diagnosis	Red	Blue: long term	Blue: short term	Grey: long term	Grey: short term	Exceptionality	Not approved (rejected)	Awaiting Panel decision	Panel decision not recorded
Ab-mediated rejection (solid organ)	4			1	53			3	
Ab-incompatible transplantation			1		24				
CMV-induced pneumonitis following transplantation	2								
Other (transplantation)	13	2	3		49			6	

Prioritisation in the Demand Management Programme is shown by shading.

11.1 Immunoglobulin use for individual diagnoses and according to colour-coded prioritisation

The assigned Panel decisions are interesting. Apart from two patients with the only 'Red' indication in the Demand Management Programme, CMV-induced pneumonitis following transplantation, 17 patients (11%) were assigned a Panel decision of Red and a further six patients a decision of Blue.

11.2. Immunoglobulin use in diagnoses with lack of evidence of efficacy ('Grey' and 'other' indications)

The vast majority (54, 89%) of patients receiving immunoglobulin for treatment of acute antibody-mediated rejection following solid organ transplantation received it with an assigned Panel decision of Grey, matching the Demand Management Programme prioritisation. All four cases assigned a Panel decision of Red were paediatric cases from a single hospital (Great Ormond Street).

Among the 13 patients with a listed diagnosis of 'other (transplantation)' assigned a Panel decision of Red, there was additional information for nine. Five were post-BMT (three had infections, two had hypogammaglobulinaemia), two had undergone heart transplantation (one had

hypogammaglobulinaemia), one had T cell ALL with hypogammaglobulinaemia and infection and one had low IgG following MUD transplant. The diagnoses provided for four of the five patients with 'other (transplantation)' assigned a Blue Panel decision were PID, antibody-incompatible transplantation, heart transplantation, and included the patient with ALL who also received immunoglobulin under a Red Panel decision.

Of the remaining 55 patients with a listed diagnosis of 'other (transplantation)', there was additional information for 27. One patient had received immunoglobulin as treatment for acute antibody-mediated rejection following solid organ transplantation, and in one patient it was probable that this was the reason for prescription of immunoglobulin. One patient had secondary antibody deficiencies and two patients had antibody-incompatible transplantation, both of which are prioritised as Grey in the Demand Management Programme. Seven patients were receiving plasma exchange in addition to immunoglobulin, according to local protocols.

11.3 Recorded use of alternatives prior to request for immunoglobulin

Corticosteroids are the most frequently tried alternative to immunoglobulin in any of the listed conditions – used in 62 patients (39%). However, the largest alternative

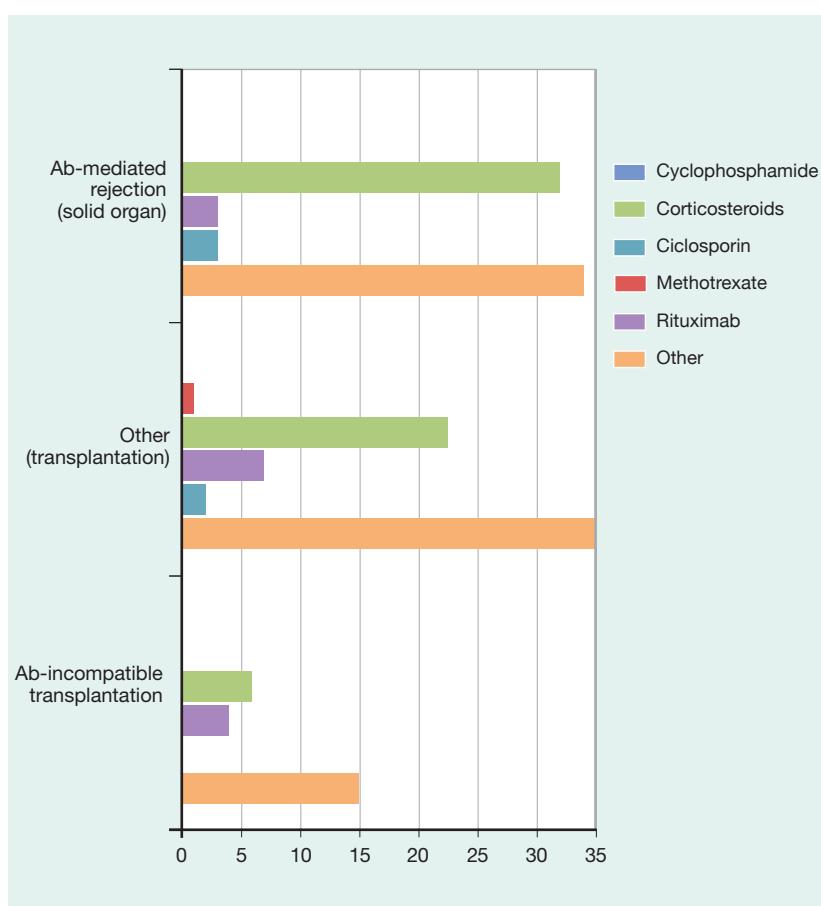


Figure 11.3 Recorded use of alternatives prior to request for immunoglobulin in individual diagnoses.

Table 11.4 Recorded consideration of plasma exchange prior to request for immunoglobulin

Diagnosis	Considered but not available	Considered but patient not suitable	Tried and failed	Not applicable	Not recorded
Antibody incompatible transplantation			5	7	13
CMV-induced pneumonitis following transplantation		1		1	
Other (transplantation)		2	3	42	26
Treatment of acute antibody-mediated rejection following solid organ transplantation	4	8	28	21	

Data show number of treatment episodes where plasma exchange was considered.

category is ‘other’ – again, a breakdown of this group would be helpful. The pattern of steroid and rituximab use in the ‘other (transplantation)’ group appears to be similar to that seen in the treatment of acute antibody-mediated rejection following solid organ transplantation and antibody incompatible transplantation groups, perhaps suggesting that this large group of unspecified cases is likely to be mainly cases that ought to have been recorded in these two ‘Grey’ indications.

11.4 Recorded consideration of plasma exchange prior to request for immunoglobulin

Plasma exchange may be part of a management strategy, including immunoglobulin, for antibody incompatible transplantation. However, the data as currently presented do not allow any meaningful interpretation. Furthermore, it is not clear how such use of plasma exchange and immunoglobulin would be recorded in the options given.

Immunoglobulin therapy is important in the treatment of acute antibody-mediated rejection following solid organ transplantation, either at high dose^{1–3} or in combination with plasma exchange.^{4–7} The combination can also be used to precondition highly sensitised patients prior to transplantation.⁸ Several protocols combining immunoglobulin with plasma exchange are in use around the country, and there is anecdotal evidence that they are effective. It is important to note that immunoglobulin remains in the body for 2–4 weeks after administration. Therefore, plasma exchange should not be used in this window as it may simply remove the immunoglobulin, potentially wasting an expensive and limited resource.

11.5 Conclusions

- Immunoglobulin prescribed for transplantation represents about 2.3% of overall immunoglobulin use.

- The vast majority of this was for ‘Grey’ indications. It seems likely that poor quality of data recording accounts for the large category of ‘other’ use in this setting.
- The database will need to evolve to encompass a variety of clinical scenarios that currently cannot be accurately recorded.

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CHAPTER 12

Therapeutic plasma exchange

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Part of the remit of the Clinical Guidelines was to provide suggestions for alternative treatments to immunoglobulin (if appropriate); graded recommendations were not provided for alternatives, to avoid any sense of a hierarchy of alternative treatments. Of all the alternative treatments listed in the guidelines, therapeutic plasma exchange has the most potential to modulate immunoglobulin use by virtue of its proven efficacy in some of the highest using indications for immunoglobulin, including CIDP. Therapeutic plasma exchange is suggested as an alternative treatment to immunoglobulin for 18 of the 79 indications listed in the Clinical Guidelines; 13 of these are neurological diseases.

The data presented for plasma exchange are for Panel episodes recorded and not patient numbers. Some patients have multiple panel decisions. Thus the data shows number of treatment episodes where plasma exchange was considered.

12.1 Use of therapeutic plasma exchange

The 18 indications account for 1023 (20%) of the 5119 patients in the database. The records in the database show that plasma exchange was tried and failed in eight of these indications, and was also tried and failed in 16 indications that do not carry a suggestion for its use as an alternative to immunoglobulin in the Clinical Guidelines.

Consideration of plasma exchange as an alternative treatment to immunoglobulin was recorded for 4435 episodes. For most (3993, 90%), it was recorded as 'not applicable'. Plasma exchange was considered as an alternative treatment to immunoglobulin in 280 episodes, but it was not available for 119 and patients were considered not suitable in 161. Plasma exchange was tried and failed in 62 episodes, of which 34 carried a diagnosis for which plasma exchange is a suggested alternative.

A total of 42 Trusts considered using PE in 120 episodes, but plasma exchange was not available. In 17 of these Trusts, plasma exchange had been tried in other patients; it is not clear if the patients were treated in different centres, or whether plasma exchange was not available within the time frame that the patient required treatment. A total of 47 Trusts considered using PE in 161 episodes, but the patient was not deemed suitable. In the 30 episodes for which plasma exchange was tried

and failed in patients with neurological diseases, 16 had CIDP. In 351 cases of CIDP, plasma exchange was recorded as 'not applicable'.

12.1.1 Limitations of plasma exchange data

The plasma exchange data as presented are clearly limited and little interpretation is possible. It is important to acknowledge that the database does not provide a baseline of plasma exchange use, and does not record cases for which plasma exchange therapy was effective. For example, patients for whom plasma exchange is successful when used as a first-line alternative to immunoglobulin treatment will not be entered into the database. Patients treated with immunoglobulin and then treated with plasma exchange may also not be recorded. Further limitations to interpretation include that data entry regarding plasma exchange does not distinguish between indications for which plasma exchange is not applicable, patients for whom plasma exchange is not applicable or centres in which plasma exchange is not available. The fact that plasma exchange was recorded as 'not applicable' for most CIDP patients suggests that the database headings for plasma exchange are ambiguous and have been misinterpreted; future revision should attempt to ensure that classification is accurate and ambiguity is removed.

12.2 Therapeutic plasma exchange services in England

Currently, provision of plasma exchange service is insufficient and unevenly distributed. NHS Blood and Transplant (NHSBT) is a Special Health Authority in the NHS that provides plasma exchange services from six centres in England. Currently, there is no service provision for plasma exchange by NHSBT in London and large regions, such as Birmingham, remain out of the range of NHSBT centres. Clinicians report that in some areas, NHSBT provision is currently insufficient to meet demand.

Plasma exchange in the London area is served by 11 units across seven large secondary and tertiary care centres. An informal network across specialties and between hospitals provides some overflow capacity out of hours and at times of peak demand. Emergency plasmapheresis (24 hours, 7 days a week) for life-threatening

conditions such as TTP is extremely limited (2 centres in London). In a 2008 review conducted by Deloitte for DH, there were approximately 1600 plasma exchange procedures in London per year, but insufficient capacity leaves patients without access to the treatment. In London, the unmet demand for plasma exchange is mainly focused in neurology. The survey reported that clinicians estimate a minimum of 60 patients per year need plasma exchange but cannot currently receive treatment due to insufficient provision. A large proportion of these patients require plasma exchange for life-threatening conditions without any alternative treatment. About half of them require plasma exchange as a last resort treatment after immunosuppressant and immunoglobulin treatment have failed. There is demand for additional plasma exchange provision in neurology and haematology and it can be anticipated that expansion of plasma exchange services would further increase demand. Four of the main teaching hospitals had the largest unmet need for plasma exchange in London; these were the National Hospital for Neurology, Barts and the London, King's College Hospital and St George's Hospital, London.

12.3 Therapeutic plasma exchange services at St George's Hospital, London

At St George's Hospital, plasma exchange is used according to guidelines adapted from the recommendations of the American Society for Apheresis (ASFA).¹ Indications

for plasma exchange are categorised according to the level of evidence of benefit (Table 12.3.1). The guidance provided for therapeutic plasma exchange in neurology indications with heavy use of immunoglobulin is shown in summary below (see Table 12.3.2). Investment in the service in 2008 enabled the establishment of a 24-hour service and resulted in an immediate 70% increase in referrals for plasma exchange. In the 18-month period from April 2008 to October 2009, 780 plasma exchange procedures have been completed; 71% were for neurology and 19% for haematology indications. The close proximity of the service to tertiary neurology/ neurosurgical services and haematology services, with general and neurological intensive care units on site, provides a safe environment for acutely ill patients to be managed by the apheresis team with the appropriate specialist teams immediately available.

12.4 A neurology perspective on therapeutic plasma exchange

The plasma exchange expansion policy was discussed at the 6-monthly meeting of the British Peripheral Nerve Society (BPNS) in October 2008 and this response represents the views expressed by the BPNS at this meeting.

1. The BPNS supports the expansion of plasma exchange services in general, and especially to increase the provision of a plasma exchange service through peripheral venous access. They agree that

Table 12.3.1 Indications for therapeutic plasma exchange: ASFA categories

Category	Description
I	Diseases for which TPE is standard and acceptable, either as a primary therapy or a valuable first-line adjunct therapy. (Usually based on well-designed randomized controlled trials or on a broad and non-controversial base of published experience.) NB: this designation need not imply that TPE is mandatory in all cases.
II	Diseases for which TPE is generally accepted but considered supportive or adjunctive to other, more definitive treatments, rather than a primary first-line therapy. (Randomized controlled studies are available for some of these disorders, but in others the literature contains only small series or informative case studies.)
III	Diseases in which there is a suggestion of benefit for which existing evidence is insufficient, either to establish the efficacy of TPE or to clarify the risk/benefit (or sometimes the cost/benefit) ratio associated with TPE. (Controlled trials have produced conflicting results or anecdotal reports are too few or too variable to support an adequate consensus.) TPE may reasonably be used in such patients when conventional therapies do not produce an adequate response or as part of an IRB-approved research protocol.
IV	Disorders for which controlled trials have not shown benefit or anecdotal reports have been discouraging. TPE for these disorders is discouraged and should be used only in the context of an IRB-approved research protocol.
P (pending)	Diseases that can be treated by TPE using devices that are not available in the USA and/or do not have FDA clearance. This category is generally assigned to those diseases where the devices are being studied in Phase III trials in the USA.

TPE=therapeutic plasma exchange.

Table 12.3.2 St George's Hospital guidelines for therapeutic plasma exchange in selected neurology indications

Diagnosis	Strength of evidence	Description	Rational	Duration	Scheduling
GBS	TPE (albumin) Category I	GBS is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Typically the disease begins with symmetrical muscle weakness and paresthesia that spreads proximally (i.e., ascends). The favoured aetiology is autoimmune antibody-mediated damage to the peripheral nerve myelin.	TPE can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones (when compared to supportive management). The Cochrane Neuromuscular Disease Group review of TPE found that TPE is most effective when initiated within 7 days of disease onset.	5 procedures over 5–10 days	✓ Weekend ✗ Night ✓ Elective Weekend only if to prevent ventilation
CIDP	TPE (with albumin) Category I	Proximal and distal symmetrical muscle weakness either with or without numbness that progresses and relapses for ≥ 2 months	The presumed aetiology of CIDP is autoimmune attack on the peripheral nerves.	2–3 per week until improvement then taper as tolerated	✓ Weekend ✗ Night ✓ Elective Weekend only if to prevent ventilation
MG	TPE (with albumin) Category I	An autoimmune disease of the neuromuscular junction characterized by weakness and fatigability with repetitive physical activity.	TPE is used to remove circulating autoantibodies - usually against the acetylcholine receptor. Little evidence to demonstrate that TPE produces better clinical outcomes than immunoglobulin	5 procedures over 5–10 days Dependent on clinical scenario	✓ Weekend ✗ Night ✓ Elective Weekend if to prevent ventilation

TPE=therapeutic plasma exchange.

even for current indications there is insufficient access nationally to plasma exchange, especially with the emergence of new antibody mediated neurological syndromes, e.g., Devic's disease.

2. Many BPNS members have doubts that plasma exchange can be considered equivalent to immunoglobulin for CIDP, because of a lack of evidence on real costs, safety and therapeutic benefit, particularly in the population having regular long-term treatment. BPNS members indicated that they would unanimously prefer immunoglobulin over plasma exchange for CIDP and MMN, even if a reliable plasma exchange peripheral vein service was locally available. This is in accordance with international opinion.
3. In order to gather further evidence, the BPNS invited the DH to provide funding to support research into

the use of plasma exchange. Initially this is needed to pay for a systematic review of the existing literature and cost data, and, if considered appropriate, funding could be sought from DH to pilot the use of plasma exchange earlier in selected patients.

4. It must be noted that the equivalence or otherwise will vary among different diagnostic conditions, for example, immunoglobulin and plasma exchange efficacy may be equal in individual treatments of CIDP; MMN may respond to immunoglobulin but usually does not respond to plasma exchange (and may be worsened by plasma exchange); Devic's disease may respond to plasma exchange but usually not immunoglobulin.
5. It is essential to get clarification of the national tariff and who pays for the cost of immunoglobulin and plasma exchange (the hospital, PCT or SCG). If the

- current situation remains where plasma exchange is not financially viable for the hospital, hospital managers are very unlikely to consider a business case.
6. The BPNS will not commit to a national policy of encouraging patients to have plasma exchange instead of immunoglobulin for CIDP and MMN unless better evidence becomes available but would strongly support the increase of plasma exchange nationally for second- or third-line treatment of CIDP and first-line treatment of many of the new antibody-mediated diseases.

12.5 Overview of therapeutic plasma exchange

12.5.1 National Transfusion Guidelines' overview²

Plasma exchange involves extra-corporeal processing of a patient's blood to remove large molecular-weight substances from the plasma. Such substances include pathogenic autoantibodies (e.g., autoantibody to acetyl cholinesterase receptor in MG), cryoglobulins or other abnormal plasma proteins (e.g., monoclonal immunoglobulin in Waldenstrom's macroglobulinaemia) or immune complexes (e.g., autoantibody to basement membrane in Goodpasture's syndrome). Several treatments are usually given. Typically, 30–40 mL/kg of plasma (1–1.5 plasma volumes) are removed and replaced with albumin or albumin and normal saline during each procedure. The procedure must be controlled to ensure that the patient is kept in fluid balance, maintaining a stable, normal plasma volume. A single exchange removes approximately 75% of the patient's own plasma and the abnormal constituent in the plasma. A series of three consecutive daily plasma exchanges will remove about 95% of a circulating IgG antibody. Thrombotic thrombocytopenia (TTP) is treated by plasma exchange with fresh frozen plasma (FFP) to replace vWF cleaving enzyme and remove antibody.

It is advised that plasma exchange should normally only be considered in conditions where well-designed clinical trials or a broad base of published experience support its use. These are TTP, GBS, CIDP and renal disease with antiglomerular basement membrane antibody. Other conditions in which plasma exchange is generally accepted as having a supportive role are rapidly progressive glomerulonephritis, cryoglobulinaemia, myeloma with paraproteins and hyperviscosity, and Lambert-Eaton myasthenic syndrome. In TTP, plasma exchange must be performed with plasma as this is more effective than simple plasma infusion. For all the other conditions mentioned, plasma exchange is performed with albumin or saline.

Thrombotic thrombocytopenic purpura

The DH policy is now to use solvent-detergent FFP (SDFFP) for TTP. Precautions against thromboembolism are recommended (graduated elastic compression stockings at diagnosis and prophylactic low molecular-weight heparin once the platelet count rises above $50 \times 10^9 / L$).

Risks of plasma exchange

Risks include: bruises or haematomas at venepuncture site; inadequate vascular access, which can compromise the procedure due to low flow or thrombosis; effects of citrate anticoagulant, such as perioral tingling and paraesthesia (due to low ionised calcium); urticaria or anaphylaxis or haemolysis due to plasma infusion, fluid overload or under-replacement; and vasovagal attack.

Haemostatic changes

PT and APTT are mildly prolonged immediately after plasma exchange, due to removal and dilution of plasma proteins, but show substantial recovery within 4–24 hours. About 10–15% of the platelets are lost during each exchange. The levels of fibrinogen and other coagulation factors fall considerably by the end of the procedure; this leads to prolonged blood clotting tests, although a clinically significant bleeding tendency does

Speciality	Condition
Neurology	Acute GBS CIDP MG
Haematology	Hyperviscosity syndromes Thrombotic thrombocytopenic purpura (exchange with FFP) Cryoglobulinaemias Post-transfusion purpura
Renal	Goodpasture's syndrome ANCA-positive nephritis
Metabolic	Refsum's disease Hypercholesterolaemia

Table 12.5.1 Clinical indications for therapeutic plasma exchange listed in the National Transfusion Guidelines

not usually result. Fibrinogen and coagulation screen should be checked after the procedure, especially if any surgical intervention or biopsy is to be performed.

12.5.2 Therapeutic plasma exchange systems

Plasma exchange has traditionally been performed with centrifugation devices that were used in blood bank-related procedures, offering the advantage of allowing selective cell removal. Plasma exchange can also be undertaken by filtration using a highly permeable filter with standard haemodialysis equipment. The machine is used in its “isolated” ultrafiltration mode, bypassing the dialysate proportioning system.³ This is the approach taken in many renal units and, although efficacious in many clinical scenarios, the use of efficient cell separators is the preferred approach in many of the indications for which immunoglobulin is an alternative treatment (e.g., CIDP).

Effective cell separators are available on the market. The machines currently used by NHSBT are the continuous flow COBE Spectra Apheresis System from CardianBCT. This system has the flexibility to deliver cell therapy and therapeutic apheresis on one platform. In this device, blood is continuously pumped into a spinning disposable harness where separation takes place

and components are either diverted to a collection bag or returned to the patient, as required.

Another example of a continuous-flow system is the Baxter Fenwall CS3000. An example of an intermittent-flow system is the Haemonetics MCS+. Intermittent-flow machines collect blood into a bowl during the draw cycle, and separate plasma and cellular components by centrifugation. Different components are diverted to the collection bag or returned to the patient along with replacement fluid during the return cycle. This process requires a single point of access to the circulation. A number of other similar devices are available on the market.

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Research into immunoglobulin

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A significant number of publications continue to appear each year about all aspects of immunoglobulin therapy, highlighting the broad range of conditions treated with this blood product and the need for clear and up-to-date guidelines. The Centre for Immunoglobulin Therapy (www.immunoglobulintherapy.org) acts as a virtual research centre, highlighting recent research, product availability and other information regarding immunoglobulin therapies.

The Clinical Guidelines recognise the need for ongoing research, particularly given the predominance of low-level evidence for efficacy in many established indications and the increasing number of indications for which immunoglobulin as immunomodulatory or replacement therapy is used despite a limited evidence base. Indeed, as part of the guideline development process, stakeholders were asked to make suggestions for future research, and these can be found as an appendix to the guidelines.

Although randomised trials and systematic reviews are the evidence of choice in assessing clinical efficacy, there are a considerable number of questions that could be answered by relatively simple and inexpensive pragmatic research. These include the relative efficacy and safety of administering immunoglobulin at a higher dose over a shorter time period and undertaking efficacy assessments between immunoglobulin courses to assess and confirm the impact of the treatment on the disease course. The hope is that the database can contribute to this pool of knowledge and influence clinical practice. A key consideration currently is the incomplete infusion data recorded and the limitations that this places on accurate data interpretation.

13.1 Current state of immunoglobulin research and development

Several new immunoglobulin products were launched in 2009, typically of higher concentration (10%) and incorporating an increased range of viral inactivation steps. Examples include Felbogammadif (Grifols), Gammaplex (BPL), Octagam 10% (Octapharma) and Privigen (CSL Behring). New subcutaneous products are also in

the pipeline from several manufacturers. This has resulted in the phased withdrawal of some of the older, lower IgG-concentration products. Studies by manufacturers suggest that the newer products are associated with lower adverse event rates, and future National Immunoglobulin Database Annual Reports will address this specific area in more detail. Of particular interest is the concept of reactions occurring during product changes, with much anecdotal experience from experts but little in terms of published evidence¹ – a situation which is likely to be clarified in the next iteration of this Report.

One argument sometimes used in support of changing brands in an individual patient is that there are no clear brand-specific differences between products, and studies to assess differences are very unlikely to obtain industry sponsorship. However, the mechanisms of action of immunoglobulin therapy continue to be studied. New mechanisms have been discovered recently which suggest that there could be theoretical differences between products. One mechanism is the effects of sialylation of the N-linked glycans in the Fc region of IgG, which modulates the anti-inflammatory properties of immunoglobulin therapy in animal models.² Studies of the degree and type of glycosylation of different commercial immunoglobulin products undertaken via the Centre for Immunoglobulin Therapy have confirmed that there are glycosylation differences between products, although comparative effects *in vitro* and *in vivo* have yet to be confirmed (Khan et al, submitted for publication). As further mechanisms of action are uncovered, additional approaches to enhance efficacy and to target therapy more effectively may come to light. One example is the ability of dopamine agonists and antagonists to modulate Fc receptor (FcR) expression density. A study of the effects of these drugs on serum immunoglobulin levels and FcR effects is due to start soon (WAC Sewell, personal communication), and may suggest an adjuvant role for these drugs in patients receiving immunoglobulin therapy.

Conservation of immunoglobulin supplies requires that alternatives to immunoglobulin therapy be used whenever possible. Further research in this field continues across the broad range of diseases in which immunoglobulin is used. One particular concern is the

limited availability of plasma exchange facilities in the UK (see Chapter 12). Data from this report will inform Commissioners about the importance of supporting such resources, which may play a crucial role in immunomodulatory treatment during any future immunoglobulin shortage.

The effects of any shortages of immunoglobulin will depend partly on the products affected. For replacement therapy, the newer subcutaneous products are increasingly used, mainly for primary immunodeficiencies. The likely arrival of new subcutaneous products in the near future, as manufacturers update products in a similar way to the newer intravenous products, is likely to further increase the proportion of patients on subcutaneous therapies. Early work from the USA investigating the potential for daily subcutaneous therapies looks promising; this would obviate the need for expensive pumps and other equipment, but needs to be investigated more thoroughly to ensure patient safety and acceptability in a UK cohort.

Immunomodulatory treatment with high-dose immunoglobulin (typically 2 g/kg given monthly) is very dependent on patient weight. Various proposals have attempted to reduce immunoglobulin dosages by prescribing on the basis of ideal, rather than actual, body weight, on the grounds that IgG is not lipid soluble. Such proposals remain experimental, and there is little evidence to support this strategy although it is a sensible area for future research. Work from the Centre for Immunoglobulin Therapy in conjunction with the an audit from the UK Primary Immunodeficiency Network has modelled serum immunoglobulin levels in relation to height, weight and body mass index, with little evidence of a firm relationship between body size and dose in terms of IgG concentration (submitted for publication).

Future studies of immunoglobulin therapy in different conditions need to be carefully tailored to answer appropriate clinical questions, many of which have been highlighted by this Report. Use of immunoglobulin in sepsis has been extensively debated in the past, sometimes without recognition of the side-effects of immunoglobulin therapy, which could seriously limit use in this area.³ Further evidence is beginning to demonstrate the effects of concurrent infection on immunoglobulin side-effects (Khan et al, submitted for publication). The approach of the Intensive Care Network Audit and Research Centre in undertaking extensive modelling studies prior to investment in large clinical trials of immunoglobulin therapy is commendable.

New indications for immunoglobulin therapy may seriously threaten the existing immunoglobulin supply if additional studies are not undertaken. Early work on Alzheimer's disease demonstrated small changes in surrogate markers of dementia, but widespread indiscriminate use of immunoglobulin for this indication would completely destabilise the UK's immunoglobulin supply (Alzheimer's is prioritised as Black by the Demand

Management Programme). It is reassuring that further work in this area is concentrating on developing monoclonal antibody therapies rather than encouraging widespread use of polyclonal immunoglobulin. Even rare disorders may threaten supply if used in times of shortage. Small studies of immunoglobulin use in mothers who have lost children to neonatal haemochromatosis have advocated massive doses of immunoglobulin (1 g/kg every week) without comparison to conventional immunomodulatory doses. More rational prescribing would at least build up a stronger evidence base with which to inform future editions of the Clinical Guidelines.

13.2 Review of ongoing clinical trials investigating intravenous immunoglobulin

The European Medicines Agency provides a detailed guideline on setting up clinical trials of immunoglobulin [Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)(CPMP/BPWG/388/95 rev. 2)], which describes the information to be documented when an application for a marketing authorisation for intravenous immunoglobulin is made, including biological data, pharmacokinetics, clinical trials and patient follow-up.

There are 26 clinical trials listed in the WHO International Clinical Trials Registry Platform that are currently recruiting patients for treatment of specific diseases with intravenous immunoglobulin. Most of these are investigating immunoglobulin treatment for diseases that are established indications for immunoglobulin, including 13 studies on diseases prioritised by the Demand Management Programme as Red (PID, ITP, Kawasaki disease, alloimmune thrombocytopenia, CMV pneumonia after renal transplantation and GBS) and three in those prioritised as Blue (bullous pemphigoid, Rh haemolytic disease and MMN). Two ongoing clinical trials are investigating Alzheimer's disease and one is assessing unexplained secondary recurrent miscarriage (currently both 'Black' indications in the Demand Management Programme); eight studies are investigating diseases currently unlisted in the guidelines (resistant neuropathic pain, multiple system atrophy, sickle cell pain crises, Sydenham's chorea, primary trigeminal neuralgia, neuroblastoma, idiopathic cardiomyopathy and primary amyloidosis). There are no ongoing trials in 'Grey' indications.

A clinical trial in neonatal sepsis, currently a 'Black' indication in the Demand Management Programme, has recently been completed. The International Neonatal Immunotherapy Study (INIS) was an international multicentre randomised controlled trial evaluating the use of non-specific intravenous immunoglobulin in addition to antibiotics in babies with suspected or proven

sepsis. The last baby was due to be assessed on 16th November 2009. The follow-up phase will continue until all the data have been collected. These results will be reviewed by the Steering Committee upon publication.

13.3 Research questions in areas of high immunoglobulin usage

13.3.1 Rituximab in CIDP

CIDP accounts for one of the largest numbers of patients ($n=466$) and greatest volumes (228,500 g) recorded in the database; this equates to a cost of more than £8 million to the NHS. The enormous volume of use, daunting cost and recognition that conventional alternative treatment options, including corticosteroids and plasma exchange, often fail identifies CIDP as a prime candidate for the development of safe and effective new treatment options. Rituximab, a monoclonal antibody targeting CD20, is the most promising of the new biologic therapies, especially for cases where IgM autoantibodies are pathogenetically involved. The National Hospital for Neurology and Neurosurgery has proposed the RICE (Rituximab In CIDP Efficacy) study, which includes a cost-effectiveness analysis as part of the protocol.

It is anticipated that RICE will run for 18 months per patient and take 3 years to complete. Patients will be recruited when their disease is considered optimally treated with immunoglobulin. They will then be withdrawn from immunoglobulin to ensure that they still require immunoglobulin (as judged by a decline in ONLS) and that the immunoglobulin interval required is 6 weeks or less. They will then be re-started on their usual regimen for three cycles to stabilise them to a baseline and then randomised to rituximab or placebo. Assessments will be performed over 24 weeks to identify any change. At 24 weeks following rituximab, patients will be withdrawn from immunoglobulin therapy again and their immunoglobulin requirement assessed following withdrawal (% in remission, time to relapse, immunoglobulin requirement) over the next 24 weeks.

13.3.2 Secondary antibody deficiencies and treatment of acute antibody-mediated rejection following solid organ transplantation

Two of the top 10 diagnoses by volume of use are prioritised by the Demand Management Programme as Grey: secondary antibody deficiencies and treatment of acute antibody-mediated rejection following solid organ transplantation. Secondary antibody deficiencies are commonly related to immunosuppressive pharmacotherapy, as noted in the Clinical Guidelines, and the evidence base for efficacy is generally weak. The situation for antibody-mediated rejection following solid organ

transplantation is less clear cut, with use seen particularly in patients undergoing kidney transplant. Certain SHAs, for example the East of England, have indicated that, according to local agreement, pretreatment for antibody-incompatible transplantation and antibody-mediated rejection following solid organ transplantation should be managed under the Demand Management Programme as Blue indications. Clearly, there would be benefit in generating a research base to assess the efficacy of immunoglobulin in these indications.

13.3.3 Plasma exchange

As described in Chapter 12, therapeutic plasma exchange has the most potential to modulate immunoglobulin use by virtue of its proven efficacy in some of the highest-using indications for immunoglobulin, including CIDP. Therapeutic plasma exchange is suggested as an alternative treatment to immunoglobulin for 18 of the 79 indications listed in the Clinical Guidelines; 13 of these are neurological diseases. These indications account for about one-fifth of the 5119 patients in the database. Clearly, additional research on the efficacy and safety of plasma exchange as an effective alternative to immunoglobulin is a priority. This would include research into the relative benefits of the different devices available on the market to perform the procedure.

13.4 Research questions in rare disorders

One hope of the database that has not come to fruition is the accumulation of evidence of efficacy for rare disorders. Such data are currently so patchy that concrete conclusions cannot yet be drawn. However, the Report at least illustrates the numbers of patients receiving immunoglobulin for rare disorders, and should encourage appropriately focussed clinical trials in the future.

13.5 Defining efficacy parameters for immunoglobulin

As part of the Demand Management Programme, Panels were encouraged to request up to three parameters by which efficacy could be determined in each patient (e.g., platelet count in patients with ITP), but the assessment of the outcome of immunological treatment is difficult to address. For example, some neurological conditions, such as the neuromuscular diseases CIDP and MG, have clearly measurable validated outcomes (impairment, disability and handicap), but for others, validated efficacy outcomes are not easy to define.

The Australian approach to tracking the efficacy of prescribed immunoglobulin offers insights into how this issue might be addressed in the future. An overriding consideration in the Australian guidelines is that 'for ongoing therapy, the achievement of measurable clinical outcomes is a requirement and IVIg should not be continued in patients with no demonstrable clinical benefit'. The guidelines give specific criteria to provide a basis for decision making on the appropriate use of immunoglobulin in the treatment of patients with particular manifestations of disease. In addition, the guidelines state: 'Where the therapeutic role of IVIg is well established or there is emerging evidence of a role for IVIg therapy in selected patients, a structured pro-forma is provided detailing the diagnostic parameters and describing the criteria that should be fulfilled if IVIg is to be used. The criteria generally refer to matters such as patient selection, particular disease characteristics, disease severity and any requirement for other treatments to have been demonstrably unsuccessful before IVIg is considered.' In particular, for each immunomodulatory indication, qualifying criteria are described and review criteria are listed. An important aspect of the Australian system is the recognition of the need for flexibility and discretion to deal with unusual requests to use immunoglobulin in justifiable circumstances. It was argued that a system that could allow limited one-off approvals for IVIg would strengthen the overall supply and approval mechanism and obviate the need for every rare condition to be covered in their document in detail.

13.6 Changing disease prioritisation status in the Demand Management Programme

As the evidence base changes for diseases, there will be changes in the prioritisation status in the Demand Management Programme. This is also acknowledged in the Model Commissioning Policy, which states: 'the long-term goal is to reclassify grey indications as blue, black, or trial. Commissioners are committed to reclassification based on high-quality clinical evidence.' The Commissioners have provided initial details of the type of evidence that would be expected to alter the commissioning policy for treatment with immunoglobulin in a particular disease. These include: health gain, evidence of efficacy, exact patient definition, number of patients expected to fulfil the definition and anticipated cost per patient. A more detailed assessment of how such reviews will be conducted will be undertaken and communicated in 2010.

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Conclusions and database development

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CHAPTER
14

14.1 Conclusions

The aim of the National Immunoglobulin Database is to capture all use of immunoglobulin therapy in England. On 17th September 2009, the database contained records of 8572 individual patients (overall number of patients entered in the database as this report goes to press has reached about 10,000) and at this time point, 161 Trusts had enrolled in the database; 12 acute Trusts in England had not registered for the database. However, complete coverage of all Trusts is neither likely nor desirable, since some NHS Trusts never use immunoglobulin therapies (e.g., mental health and ambulance Trusts), although some specialist Trusts that would be expected to use immunoglobulin were unregistered. The number of patients entered by each Trust varies considerably (0–433 patients), reflecting in part the specialist nature of some Trusts that incorporate tertiary referral centres likely to be significant users of immunoglobulin therapy.

As the record of immunoglobulin use in England gradually becomes more complete, the proportion of patients receiving lifelong therapy may gradually increase. In order to address incomplete data capture, two different approaches may be deployed in the future. For Trusts that have entered significant numbers of patients, it will be important to ensure that data quality is high, and audits of data quality (in particular diagnostic accuracy and completeness of infusion records) would be a valuable strategy.

For Trusts that have entered very few patients, future strategies need to be directed to investigating why this is. Some centres may genuinely have very few patients receiving immunoglobulin therapy, but the concern is that centres with very few patients in the database may not be keeping up with data entry or, worse, not using a Panel approval process. Individual enquiries of these Trusts, rather than an audit, may produce a better return, particularly if support can be offered in terms of sharing good practice used by Trusts of similar size and case mix.

Data quality remains an important issue. In each specialist area, it is apparent that the same condition may have been entered against a variety of priority

categories (Red, Blue, etc.). In some cases, this may be because the diagnosis at the time did not quite fulfil criteria described in the Clinical Guidelines. For example, a request for immunoglobulin therapy for a patient with ITP who had perfectly acceptable platelet counts, yet was about to undergo a neurosurgical procedure for which higher platelet counts are recommended, would correctly be assigned a Panel decision of Grey, rather than Red. However, the impression is that many centres did not assign priority categories in a consistent manner, and more explicit advice could be issued in the future to reduce this disparity. It is now over 2 years since the production of the 1st edition of the *Clinical Guidelines for Immunoglobulin Use*, and it is clear that these will now need to be amended in the light of new evidence. Individual specialists have referred to this within their own chapters of this report, but a clear example would be the puzzling discrepancy between advice for CLL and non-Hodgkin's lymphoma in the Clinical Guidelines.

The quality of data in the diagnosis category also remains problematic. Two areas are of particular concern. First, since some disorders are not recorded by name in the available pre-set options in the database, these have been recorded in different ways. Individual centres have often clarified the data using the comments section, but this does not readily facilitate analysis unless each comment entry is scrutinised individually. The production of individualised data entry forms for particular conditions may help to resolve this.

The second concern is where a patient has co-existing conditions, which is particularly common in some of the immunological disorders, for example, a patient with CVID who also develops ITP. In this setting, we could consider two different entries, one for the long-term replacement immunoglobulin therapy for the immunodeficiency and one for the acute use of immunomodulatory therapy. Some degree of overlap will remain, but the number of patients involved will be small.

The overall number of patients entered in the database at the time of data extraction was 8572. This represents a significant effort on behalf of most acute Trusts, and clinicians, pharmacists and others should be congratulated on this achievement.

Of some concern, however, is the incompleteness of data on the quantity of immunoglobulin used. Two areas have been problematic: first, the amount of product entered at registration of the patient request and, second, the absence of individual infusion data. The first issue comes about when Trusts enter a request for therapy prior to the Panel decision. In some situations, the exact dose requested has been left blank, presumably as the Panel is also being asked to give advice about the relevant dose. In this group of patients, the current analysis omits the dose of immunoglobulin assigned to these patients. Making this field mandatory at the point of data entry would resolve this issue, particularly if used in conjunction with an explicit entry for duration of therapy. Various Panels are currently recommending different durations of trials of therapy, so it is not currently possible to make an estimate of eventual total use for patients undergoing therapeutic trials of immunoglobulin.

The issue of absent individual infusion data is disappointing. Total immunoglobulin use can be derived from the individual registration details, particularly if the planned duration of therapy is recorded in the future. However, a vital aspect of the recording of individual infusions is the ability of the database to track batches. Problems with contaminated blood products have occurred in the past with hepatitis C and with new variant Creutzfeld-Jacob disease (vCJD). In each of these crises, individual hospitals found it extremely difficult to identify patients who had received those batches, and even harder to estimate the total dose of product that each patient had received. The clinical community welcomed the introduction of the National Immunoglobulin Database because it would finally address this issue of batch tracking at a national level, and it was an important driver in promoting acceptance of the Demand Management Programme. However, difficulty in entering individual batch numbers has been considerable. Several approaches are possible to address this. An easy first step would be to use drop-down menus for batch number data entry, rather than free text fields. This would immediately remove the possibility of erroneous data entry. Plans are under way to develop bar coding of individual products, but the wide variety of barcode formats used internationally makes this very difficult, as would the expense of equipping all relevant units with barcode readers and software. A third approach has been studied in Oxford recently, using pharmacy-produced bar codes for individual boxes of products that incorporate additional safety information (e.g., expiry date, etc.). Early results have been promising (Janet Burton, personal communication).

Initial plans for the database were designed using a model similar to blood product transfusion tracking currently used in all NHS hospitals. This approach was not communicated clearly in the early peer-review process of the database design, so was dismissed as being

'too complicated'. On reflection, since all hospitals are already familiar with the processes involved in batch tracking of blood products, using similar processes (whether barcode- or paper-based) may facilitate more complete data entry in the future and should be given serious consideration in future updates of the database.

The volume of immunoglobulin use entered into the database for the 1-year period covered in this report (18th September 2008 to 17th September 2009) is 1200 kg for 5119 patients. This is likely to be a significant underestimate, particularly since the PASA allocation amounted to almost 2300 kg. This is due to both incomplete data and the difficulties of capturing each infusion event. The estimated average use per patient given in this report may also be an underestimate.

Where the database has not been so successful is the capture of data regarding efficacy of immunoglobulin. Panels were encouraged to request up to three parameters by which efficacy could be determined in each patient (e.g., platelet count in patients with ITP). The purpose of this exercise was both to obtain preliminary data about efficacy in various conditions (fully accepting that lack of diagnostic criteria and other issues would make this a very crude analysis) and to provide feedback to individual Panels about the quality of their decision making. If Panels repeatedly approve indications prioritised as Grey by the Demand Management Programme and the treatment is largely ineffective, this statistic should improve Panel decision making. Given that we now know that most prescribing has been for approved conditions, a more pragmatic approach may now be to abandon efficacy tracking for conditions prioritised by the Demand Management Programme as Red or Blue. Commissioners will want to know that Panels are making effective decisions, so retaining efficacy tracking for 'Grey' indications only is a logical development for the future. To facilitate this, consideration should be given to predefined efficacy monitoring parameters for selected conditions, accepting that this is not possible for the entire gamut of human disease!

Although many Trusts have made sterling efforts to enter complete data, it is apparent that this has not been possible in most cases. Many cite lack of resources, and begrudge the presumption that this process is something that pharmacy departments will just 'cope with'. Both Commissioners (see Chapter 3) and clinicians are very keen that the process continues, but urgent consideration needs to be given to facilitating Trusts in entering complete data in a timely fashion. The linking of reimbursement for immunoglobulin expenditure to database entry, as proposed by the Commissioners, needs to be balanced with a 'carrot'. An example that has been used to good effect by the Yorkshire and Humber SCG in 2009/10 was including data completion as a goal within local CQUIN schemes, making a small proportion of provider income (0.5% of contract value in 2009/10)

conditional on achievement of this locally agreed quality improvement and innovation goal.

One disincentive to data entry is the current perception that the Demand Management Programme is not currently needed as supplies of immunoglobulin are good and there have been no batch recalls in the last year. However, this situation could change rapidly; immunoglobulin manufacturers continue to change hands in a global market and are no strangers to the financial hardships affecting all companies. The finding of BSE in cattle in a plasma donor country could alter procurement practices overnight. To this end, the utility of the National Immunoglobulin Database now needs to be tested in a series of exercises, both to determine the efficacy of the batch-tracking process and to determine the scale of the impact of loss of a manufacturer(s). The ability of the database to rapidly identify the number and total exposure of patients to a specific batch, and to quantify the amount of product being used within each prioritisation category (Red, Blue, Grey), will enable robust and effective contingency measures to be put in place.

With the deployment of the Model Commissioning Policy, examination of the utility of this commissioning process will be as important as ensuring adequate data quality in the database. After all, there is little point in a process designed to ensure equitable use of immunoglobulin if it is compromised by geographical differences in interpretation of the rules. SHAs need to appreciate that the Demand Management Programme was designed to facilitate fair use of immunoglobulin in times of shortage, not to deny desperately ill patients effective therapy. Since many of the diseases treated with immunoglobulin vary considerably in severity and presentation, it is essential that the role of the Panel in deciding N=1 trials of individual cases is retained, and that the concept that 'grey indications don't need immunoglobulin' is very firmly squashed.

14.2 Suggested improvements to the database

There has been confusion about the terminology in the database, and some information is not readily extractable. Therefore, it has been suggested that the fields for 'Indication' (i.e., the primary diagnosis, for which immunoglobulin is being prescribed), 'Panel decision' (based on colour-coded prioritisation) and short- or long-term therapy should be separated. In addition, separate fields for primary and secondary diagnoses have been suggested, as has a system to limit the choice of Panel decision to those recommended in the Clinical Guidelines.

It may be useful to make it mandatory to complete the field for the intention to use immunoglobulin as short- or long-term therapy. Where treatment has been listed as short term but infusion data show that it is being administered long term, a system warning could be generated indicating that a further Panel decision is required.

For some patients who have received more than one course of immunoglobulin, several Panel episodes have been opened concurrently. As a new Panel episode is only required if it is necessary to obtain a new decision from the Panel (e.g., for a different disease episode), it has been suggested that the database not allow a new Panel episode to be opened until the current episode has been closed. Panel episodes could have a defined duration, depending on the selection of short- or long-term treatment.

Consultant Specialty has not been useful and may be dropped from future iterations of the database. Instead, diagnoses would be linked to specific specialisms, as described in the Clinical Guidelines.

To help Commissioners identify patients who fall within their responsibility, the intention is to make GP Practice code and/or NHS number mandatory. Prior to that, a reminder could appear to include this information.

A more detailed assessment of database changes will be undertaken and communicated in 2010.



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