DH Department of Health

National Immunoglobulin Database Update

April 2009

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For Recipient's Use			

INTRODUCTION

This document provides an update to all Trust Chief Executives and Medical Directors of the ongoing activities of the National Immunoglobulin Database. We recommend that all clinicians, pharmacists and members of a Trust's immunoglobulin assessment panel (IAP) are informed of the contents of this document.

As you will be aware, 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 Medical Data Solutions and Services (MDSAS) contracted to continue the database programme and to be responsible for working with a DH-sponsored database steering group to maintain and extend the solution.

This document provides an update on the uptake of the database and initial findings on immunoglobulin prescribing patterns. It also includes:

1. Updated guidance on the use of immunoglobulin for measles post-exposure prophylaxis
2. News of articles published in the *British Medical Journal* on the DH immunoglobulin guidelines
3. Information on the Model Commissioning Policy
4. An update on the immunoglobulin website

INITIAL FINDINGS FROM THE DATABASE ON IMMUNOGLOBULIN PRESCRIBING PATTERNS

The database has been operational for 9 months. There have been a number of issues with regard to its smooth operation, such as speed and complexity of data entry, but MDSAS 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.

Annual reports will be prepared from the database, and the first of these will be available by the end of 2009. In the meantime, initial data analyses have been performed. The graphs in this document show how immunoglobulin was used in the period June 2008–February 2009 (9 months), with use shown by local IAP decision, long- or short-term use and specialism. Eighty-five Trusts have contributed data, recording more than 400,000 g of immunoglobulin use.

Database Support Procedure:
All support requests, including guidelines for immunoglobulin use, data entry questions and database technical issues, should go through the IVIg support team at MDSAS. No support calls, other than username and password requests, should go directly to Dendrite (the IT vendor).

Grey indication usage

The data show that there is little use of IVIg in grey indications, which is reassuring and welcome. An important point is that some IAPs are currently managing grey indications as blue indications. **These patients should be entered into the database correctly as grey**, even if the current descion-making process does not distinguish blue from grey; this will be audited.

Immunoglobulin assessment panel decisions

An IAP decision is recorded for more than 50% of patients entered into the database, but in the remaining cases, no IAP decision has been entered. The assumption is that the patients for whom there is no panel decision (green in Figure 1) are receiving life-long immunoglobulin; all patients receiving long-term immunoglobulin

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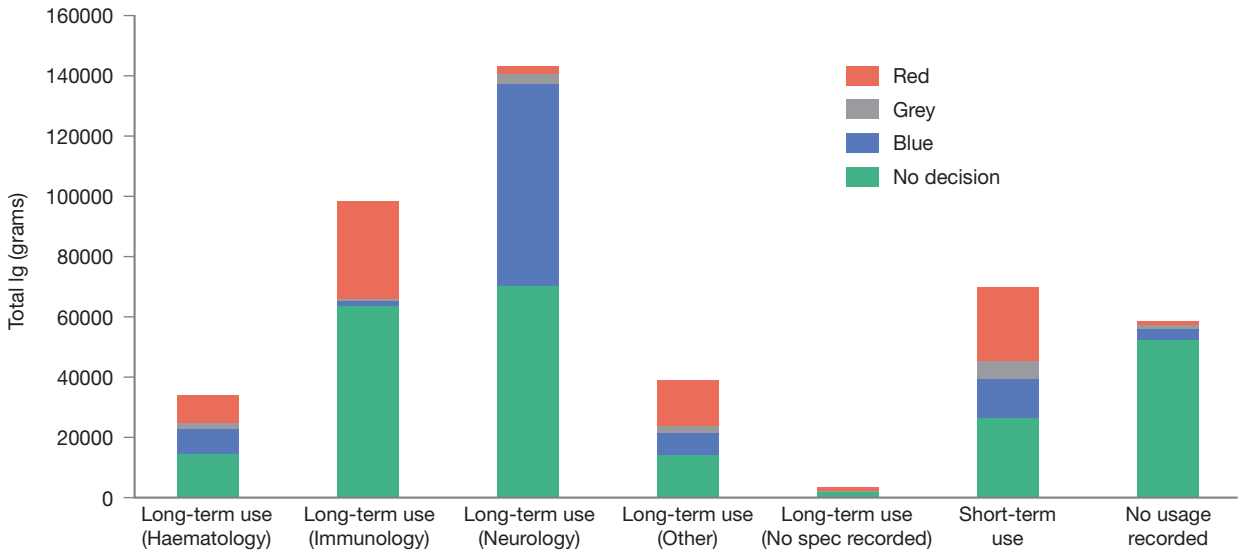
should be reviewed annually to assess disease activity and determine the best therapeutic option. This review should be seen as part of normal clinical practice. The expectation is that more patients will be considered by the local IAP over the next 4 months. By 30th June 2009, DH estimate that only 15% of patients will not have an IAP decision recorded; **this will be audited**.

As has been communicated previously, the database must contain a complete record for each patient. Entries that do not have an IAP decision listed, or that are incomplete in any way, **will have funding withheld when the commissioning policy comes into effect.**

Figure 1. Usage split by long- and short-term use and specialism, showing panel decision



Definitions

Short-term	Short-term use means ≤3 courses are expected
Long-term	Long-term use means >3 courses are expected if a trial of treatment is successful
Red	Conditions for which treatment is considered the highest priority because of a risk to life without treatment (automatic Panel approval)
Blue	Conditions for which, although the evidence base is reasonable, the priority is moderate because other treatments are available (Panel approval required)
Grey	Conditions for which the evidence base is weak (Panel approval required)
Black	Not recommended (automatic Panel rejection)

Blue indication usage and alternative treatments

More than 100,000 g immunoglobulin was used for blue indications. For many of the blue indications, alternative treatments are recommended, including therapeutic plasma exchange (TPE), and these can be recorded in the database. Figure 2 shows that plasma exchange was not generally considered applicable for the majority of these patients. However, around 60% of blue usage was for chronic inflammatory demyelinating polyneuropathy, which suggests that TPE, an alternative offered by the Clinical Guidelines, is not being considered for these patients; the most common alternative treatment tried was corticosteroids (Figure 3).

Figure 2. Consideration of therapeutic plasma exchange in blue indications

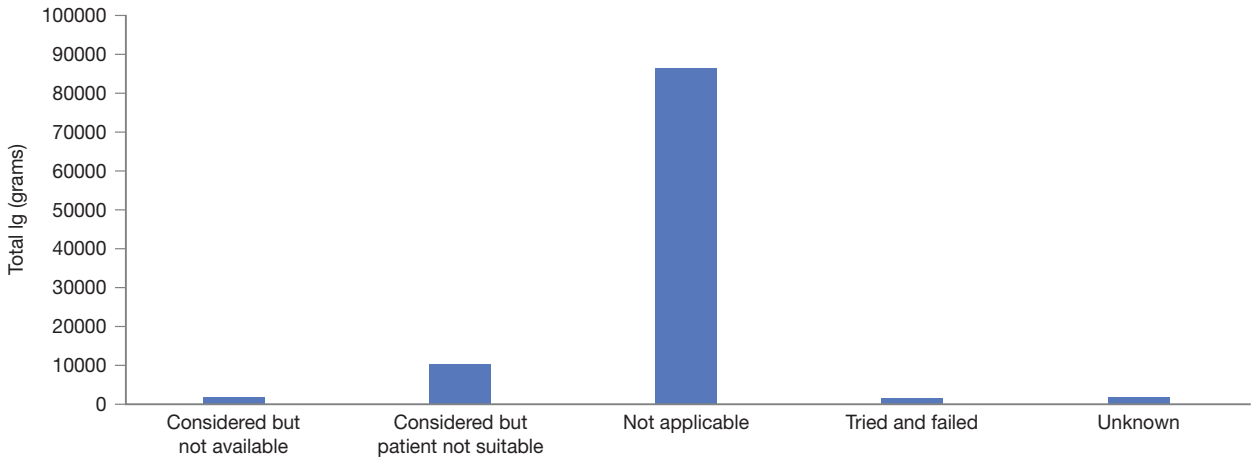
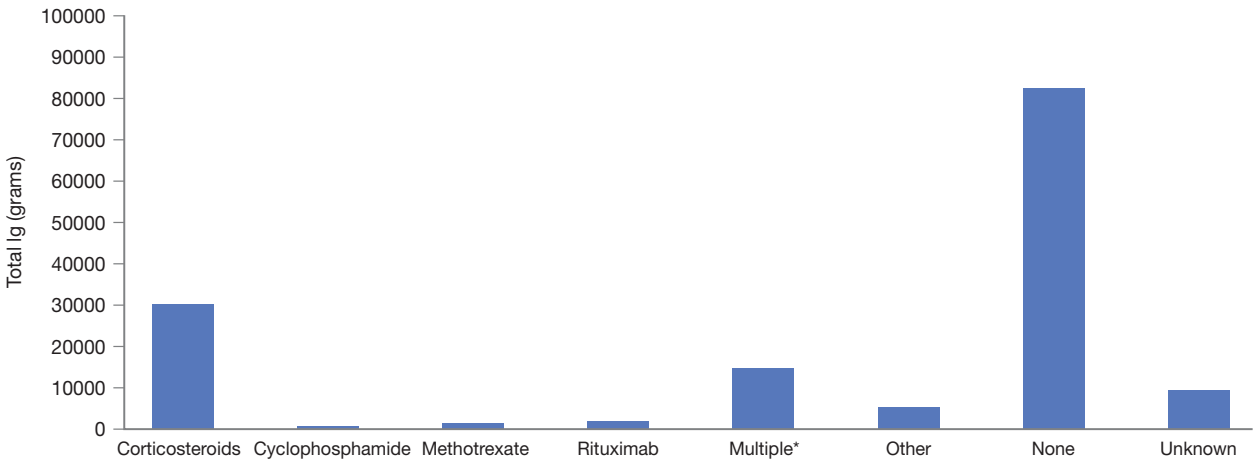


Figure 3. Alternative therapies to immunoglobulin tried in blue indications



UPDATED GUIDANCE ON THE USE OF IMMUNOGLOBULIN FOR MEASLES POST-EXPOSURE PROPHYLAXIS

With regard to measles post-exposure prophylaxis for infants, pregnant women and patients who are immunosuppressed, due to the high number of measles cases currently occurring, shortages of human normal immunoglobulin may be experienced. In such a situation, the Health Protection Agency (HPA) has issued revised guidance giving recommendations of when to use MMR vaccine or immunoglobulin as an alternative.

As the evidence base for the use of immunoglobulin is weak, the Expert Group on IVIg has decided that the current guideline recommendation should remain unchanged as a grey indication. However, commissioners will not seek prior approval in such cases before treatment, but will continue to insist on database entry and completion. DH will closely monitor uptake of IVIg for this clinical scenario to ensure adequate supply for red indications. Access the HPA guidance at www.hpa.org.uk.

SUMMARY OF THE HPA GUIDANCE

Susceptibility

Susceptibility, and therefore the approach to prophylaxis, is based on prior exposure to natural measles or vaccine and the reason for any immunocompromise (Tables 1 and 2). For advice on post-exposure prophylaxis in pregnant women and healthy infants, refer to the full HPA guidance.

Dosing

For immunocompromised patients who require measles IgG antibody testing, this should be possible within 1 working day of receiving the serum sample. The protective dose can probably only be administered by either intravenous or subcutaneous infusion. A protective dose of approximately 11 IU/kg measles antibody should be achievable using 0.6 mL/kg subcutaneous immunoglobulin or 0.15 g/kg IVIg.

Table 1 Use of IVIg in immunosuppressed contacts of measles

Treatment	Birth year	Patient status
Assume immune	Before 1970	Group A immunosuppressed patients + previous measles infection
Test and issue only if measles antibody negative or equivocal	Before 1970	Group A immunosuppressed patients – previous measles infection
	1970–1990	Group A immunosuppressed patients + previous measles infection
Test and issue if measles antibody negative or equivocal. If not possible to test within 6 days of exposure, offer IVIg	1970–1990	Group A immunosuppressed patients – previous measles infection
Test and issue if measles antibody negative or equivocal. If not possible to test within 3 days of exposure, offer IVIg	After 1990	Group A immunosuppressed patients + 1 or 2 measles vaccine doses
Offer IVIg, ideally within 3 days	After 1990	Group A immunosuppressed patients – measles vaccination
Regardless of history and even if known to be measles antibody positive previously, test again at time of exposure Issue IVIg if measles antibody negative or equivocal If not possible to test within 3 days of exposure, offer IVIg	Any	Group B immunosuppressed patients

*Excluding patients who are already on IVIg replacement therapy for primary immunodeficiency or severe defects of cell-mediated immunity.

Based on very limited data, immunoglobulin is given up to 6 days from exposure. For immunosuppressed patients who are known or likely to be susceptible, administration should not be delayed beyond 3 days after exposure. Where exposure is recognised late, IVIg is likely to provide higher levels of measles antibody more quickly than an intramuscular or subcutaneous product.

Table 2 Immunosuppressed patients

Group A patients	Group B patients
All those with malignant disease, other than those in group B, until ≥6 months after completion of immunosuppressive chemotherapy or radiotherapy	Patients on treatment for acute lymphoblastic leukaemia within and until ≥6 months after completion of immunosuppressive chemotherapy
Solid organ transplant recipients currently on immunosuppressive treatment	Bone marrow transplant recipients until ≥12 months after finishing all immunosuppressive treatment, or longer where the patient has developed graft-versus-host disease
Patients receiving systemic high-dose steroids, until ≥3 months after treatment has stopped, including children who receive prednisolone at 2 mg/kg/day for ≥1 week or 1 mg/kg/day for 1 month. For adults, an equivalent dose is harder to define but immunosuppression should be considered in those who receive prednisolone ≥40 mg/day for >1 week	Patients with severe primary immunodeficiency
Patients receiving other immunosuppressive drugs alone or in combination with steroids, until ≥6 months after terminating such treatment	
HIV-infected individuals who do not have a diagnosis of AIDs	Patients with a diagnosis of AIDs

NEWS OF ARTICLES PUBLISHED IN THE *BRITISH MEDICAL JOURNAL* ON THE DH IMMUNOGLOBULIN GUIDELINES

A summary of the clinical guidelines was published by the *BMJ* in October (Provan D et al. Prescribing intravenous immunoglobulin: summary of Department of Health guidelines. *BMJ* 2008;337:a1831), as part of the *BMJ* Guidelines series in the Practice section of the journal. The Immunoglobulin Expert Group worked closely with the *BMJ* editors to ensure that the language used removed any ambiguity with regard to the recommendations and colour coding. The article provides a useful summary of the guidelines, and the format employed by the *BMJ* offers a clear and simple overview of the guideline, including excellent colour summary tables, which many may find more approachable than the guideline document itself. The Expert Group therefore highly recommend that this summary document is downloaded from the *BMJ* website (link provided above and on the IVIg website) and is viewed as a sister document to the main guideline.

The *BMJ*'s usual procedure in this series is to commission a commentary from independent clinicians, in this case from New Zealand (Fitzharris P, Hurst M. Commentary: Controversies in the Department of Health's clinical guidelines for immunoglobulin use. *BMJ* 2008;337:a1851). The commentators were concerned about the clarity of the definitions for immunoglobulin use, particularly the colour coding of definitions, and the complexity of the approval process. They also suggested that success requires motivated Trusts with accessible panels providing rapid responses to requests.

The Immunoglobulin Expert Group responded to this commentary in a Rapid Response (Provan D et al. The Department of Health's clinical guidelines for immunoglobulin use "seeking 'A' for efficacy"). The Group remains acutely aware of the challenge of implementing this Demand Management Programme and are working to provide good models of local Trust policies that will effectively deal with the commentators' concerns. The model commissioning policy (see below) will provide further details of how the process will operate.

The original summary generated correspondence in BMJ online on the use of immunoglobulins in chronic fatigue syndrome (CFS) and vasculitides; the responses of the authors of the Clinical Guidelines to these letters are available on the same web page. The Expert Group believe that the guidelines and the demand management plan provide a framework for all treatment decisions. In exceptional cases where reasonable evidence for the use of immunoglobulin has been provided, health commissioners would be asked to sanction funding of the treatment following approval by the local IAP.

THE MODEL COMMISSIONING POLICY

The Model Commissioning Policy for immunoglobulin provision will be published in April and will be available from the immunoglobulin website (www.ivig.nhs.uk). The aims of this policy are:

1. To target a 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
2. To operate a robust mechanism for managing and prioritising access to immunoglobulin treatment at times of short supply
3. To ensure that funding for immunoglobulin is linked to the provision of data to the national database to improve the health community's understanding of the current use of and demand for immunoglobulin

Having presented this work to the Directors of Specialised Commissioning Teams, commissioners felt that it was important to provide a clear statement of the commissioning position and the decision-making process for each category of treatment. In addition, it was also considered important that funding was linked to data provision to the national immunoglobulin database.

The development of this commissioning policy will be an iterative process and so will require an annual review. This is because there are a number of issues that still need resolving to the satisfaction of commissioners. A National Immunoglobulin Working Group, which has Department of Health, commissioner and clinician representatives, will provide advice to the National Specialised Commissioning Group on further development of the service specification. The key specifications are:

- All applications for funding, 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.

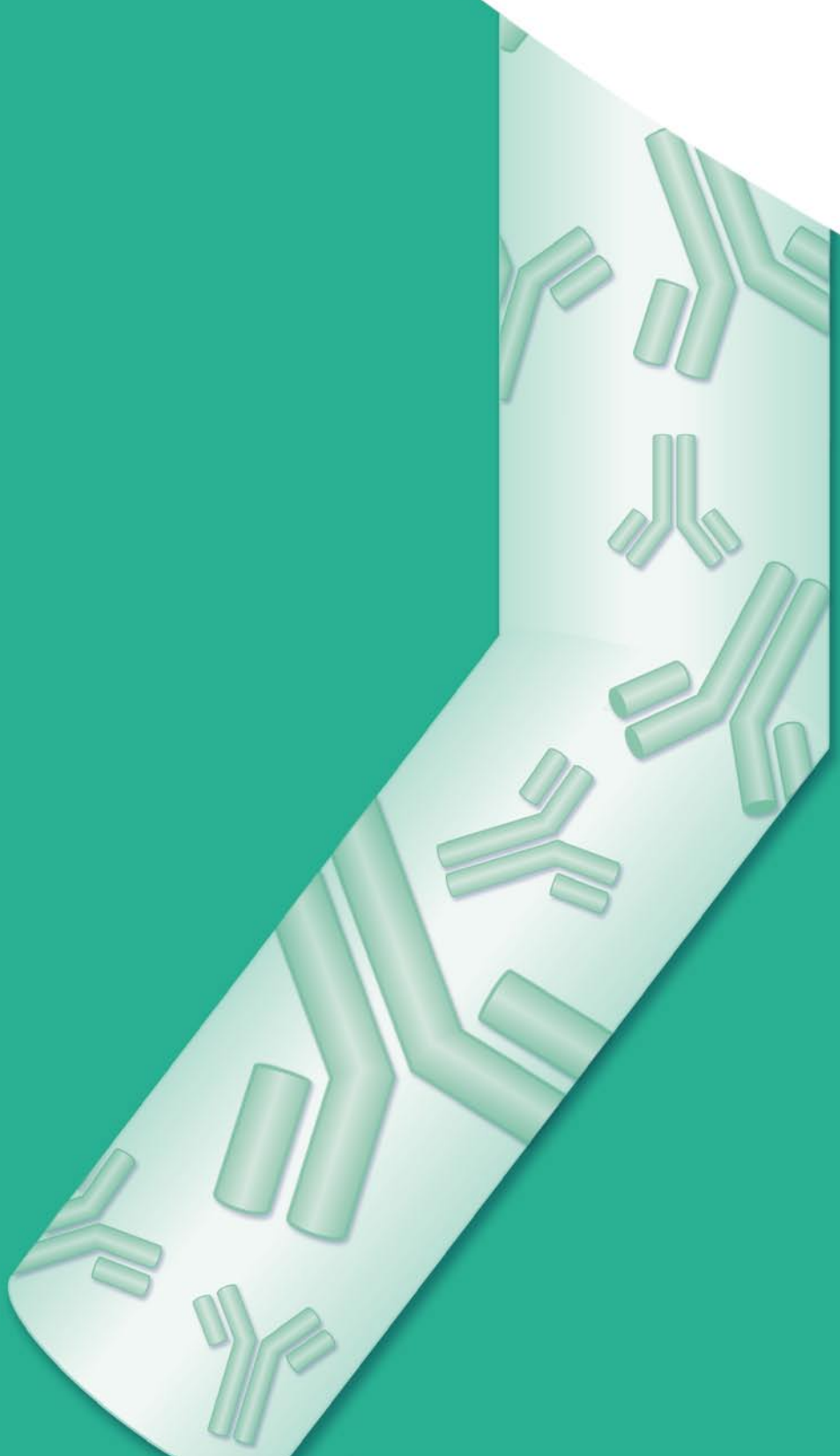
Under the commissioning policy, all immunoglobulin will be prescribed by a consultant with specialist knowledge of its use; there will be no GP prescribing. Prescribers should monitor future DH communications on any risks to supply and understand the mechanism for handling any shortages. Patients should be fully informed of arrangements for their treatment and the implications of any supply shortages.

AN UPDATE ON THE IMMUNOGLOBULIN WEBSITE

MDSAS took over the running of the IVIg website from MMRx Consulting in July 2008. The website address was updated (www.ivig.nhs.uk) and new content added. The focus of the homepage is currently the database, with tabs at the top of the page providing access to:

- The Clinical Guidelines, Demand Management Plan and stakeholder review documents (Clinical Info)
- A patient guide to demand management (Patient Info)
- Presentations at meetings held in 2007 and 2008 (e-Learning)
- A list of the stake holders involved in the 2008 review, with links to their websites (Links)
- Answers to frequently asked questions (FAQs)
- Details of how to view documents online or order hard copies (Help)

Further changes are planned, including communicating the Immunoglobulin Model Commissioning Policy and provision of a simple process to report shortages, which will ensure that all the relevant parties are promptly informed.



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