

# A PRACTICAL APPROACH TO ANTIBODY DEFICIENCY SYNDROMES

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## ABSTRACT

Antibody deficiency diseases are common collectively. The clinical presentation of these disorders is extremely variable and they affect many different organ systems; hence these patients present to a variety of medical and surgical specialists. Patients suffering from antibody deficiency are susceptible to significant, recurrent infections and if diagnosis and implementation of therapy is delayed are likely to experience significant morbidity and even mortality. It is therefore important that a broad range of physicians and surgeons are able to recognise the symptoms and signs of primary antibody deficiency, so that they are able to order and analyse basic immunology laboratory investigations. This will expedite referral to an appropriate specialist who is able to manage the affected individuals in the long term. The classification, clinical presentation, laboratory investigation and clinical management of such patients are reviewed.

For the purposes of clinical utility, these diseases are classified according to the pattern of immunoglobulin deficit identified. Increasingly though, as the molecular cause of individual diseases is elucidated, these diseases are being classified according to the molecular basis – this approach, while fascinating, is of little practical value to this discussion.

One can conceptualise disorders of antibody production in two broad categories: (i) disorders in which B-lymphocytes have developed normally, but are functionally deficient; and (ii) disorders that have interrupted normal B-cell development. In the former, circulating B-cells are found in the blood and secondary lymphoid tissues are present and may even be enlarged, e.g. common variable hypogammaglobulinaemia and the hyper IgM (HIGM) syndromes. In the latter, however, because of maturational arrests at various stages of development, mature B-lymphocytes are not found circulating in the peripheries and there is paucity of lymphoid tissue (absent tonsils, lymph nodes, etc.). Examples of the latter conditions are X-linked agammaglobulinaemia, and the disorders of the pre-B-cell receptor (15 and Igα).

Disorders of B-cell maturation and function are listed below (Table I), together with their molecular defect and chromosomal location where known.

## INTRODUCTION

Primary immune deficiency syndromes have long been relegated to the fine print of medical and paediatric texts in the misbelief that they are rare and are managed exclusively by sub-specialists in academic institutions. On the contrary, however, inherited disorders of the immune system are collectively not uncommon<sup>1,2</sup> (approximately 1:5 000 population) and patients suffering from these diseases are seen every day by a wide spectrum of physicians and surgeons. No single group of primary immune disorders illustrates the diversity of clinical presentations more than those affecting the production of specific antibodies – so-called humoral immune deficiency. Humoral immune deficiency predisposes affected individuals to a wide spectrum of illness, including chronic sinopulmonary disease, chronic inflammatory gastroenteropathy and gastrointestinal infections, severe neurological disease, skin disorders, auto-immune arthropathies, auto-immune haematological cytopenias and an increased risk of predominantly lymphoid malignancies. Missed or delayed diagnosis leads to significant morbidity and mortality, hence it is essential that all physicians have at least a working knowledge of the clinical presentations, laboratory investigations and therapies available to this group of patients.

## CLASSIFICATION/DEFINITION

Humoral immunodeficiency may be defined as a diverse group of genetic disorders affecting many components of immunological development and function where the final common pathway is the inability of B-lymphocytes to produce sustained, high-quality antibody responses to antigens.

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**Table I. Classification of primary antibody deficiency disorders**

Antibody deficiencies	Gene defect (chromosomal)
• X-linked agammaglobulinaemia	btk (Xq21.3)
• X-linked agammaglobulinaemia with growth hormone deficiency	
• AR agammaglobulinaemia	
– $\mu$ heavy chain deficiency	IGHM (14q32)
– $\delta$ deficiency	IGLL1 (22q11.22)
– IgA deficiency	mb-1 (1q13.2)
– BLNK deficiency	BLNK (10q23.22)
• Hyper IgM (HIGM) syndromes	
– XL (HIGM1)	CD40L (Xq27)
– AID defect (HIGM2)	AID (?12p13)
– CD 40 deficiency (HIGM3)	CD40 (20q12-q13.2)
• X-linked anhydrotic ectodermal dysplasia with immune deficiency	IKK $\gamma$ gene
• Immunodeficiency with thymoma (Good syndrome)	
• Impaired polysaccharide responsiveness (selective antibody deficiency)	
• Selective IgM deficiency	
• Selective IgE deficiency	
• Selective IgG subclass deficiencies	
• Selective IgA deficiency	
• Antibody deficiency with normal Ig's	
• Common variable immunodeficiency	
• Transient hypogammaglobulinaemia of infancy	

### CLINICAL SPECTRUM

Although all humoral immune deficiency disorders share the inability to produce effective, long-lasting specific antibodies, there is a wide spectrum of clinical presentations (Table II). Certain features are common to all humoral immune deficiency diseases; notably recurrent, severe sinopulmonary infections caused by common extracellular pathogens *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Mycoplasma* spp. It is not uncommon for these patients to already have significant end organ damage at the time of diagnosis, most often bronchiectasis, suppurative otitis media or chronic sinusitis. There are however, certain infections and presentations that are more highly suggestive of one disease than another; these features are presented in Table II.

### DIAGNOSIS

The aims of investigation of patients with suspected immunodeficiency are: (i) to identify infectious, metabolic and nutritional abnormalities that may have occurred as a result of the immunodeficient state; (ii) to establish the immunological diagnosis so that therapy may be planned; and (iii) to elucidate the molecular aetiology of the disease in order to better understand the molecular basis of the immune system and to develop more selective and effective therapeutic strategies.

A detailed discussion of the medical approach to the infected and chronically ill patient is beyond the scope of this review. It cannot, however, be too strongly stated that early and accurate diagnosis of infection coupled with aggressive antimicrobial therapy is essential in order to minimise end organ damage in this group of patients. The progressive loss of lung function associated with recurrent chest infections is the single greatest cause of mortality in the untreated antibody-deficient patient. Antibody-deficient patients are by definition unable to produce specific antibodies. There is therefore no role for the use of serological investigations when attempting to identify infecting organisms. In the immunodeficient patient, methods geared towards identifying whole organism (culture) or antigens from infecting organisms (PCR, etc.) are paramount.

Detailed family history taking is essential for the evaluation of antibody-mediated immunity. When a molecular or gene defect is identified, family members should also be evaluated to determine inheritance patterns, carrier status and the presence of immune system abnormalities.

Central to the investigation of antibody deficiency syndromes is the evaluation of serum immunoglobulin levels and the assessment of the patient's ability to make long-lasting specific antibody responses to commonly encountered antigens. When assessing serum immunoglobulin levels, physicians should always refer to age-corrected reference ranges and should be aware of the developmental limitations that very young patients have in respect of their ability to respond to certain antigens, e.g. infants less than 2 years of age have limited ability to respond to carbohydrate antigens.

By far the most important determination of adequacy of the humoral response is the assessment of the patient's ability to make specific antibodies to a microbial pathogen or its products. To obtain a full picture of a patient's antibody production capacity, evaluation of the response to protein and polysaccharide antigens is necessary. Diphtheria and tetanus toxoid, viral vaccines, and multivalent *S. pneumoniae* polysaccharide vaccines are readily available immunising agents. In the patient with a suspected primary immune deficiency, live attenuated vaccines should never be administered. A

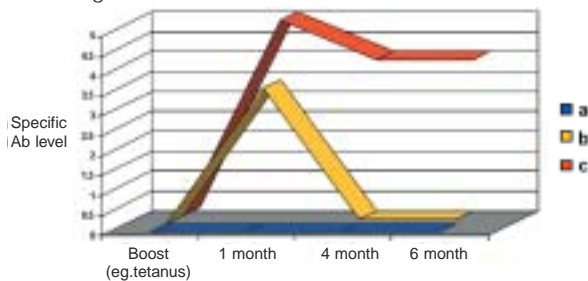
**Table II. Clinical presentation of antibody-deficiency syndromes**

Recurrent infections, usually sinopulmonary. Frequently affecting more than one site at a time. Common organisms: <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i> and <i>Mycoplasma</i> spp.	Common to all antibody deficiency diseases
Age at presentation: > 6 months of age	Most antibody deficiency diseases except CVID
Second decade of life	Most commonly CVID
<i>Pneumocystis carinii</i> pneumonitis	HIGM 1 CVID
Paucity of lymphoid tissue: absence of lymph nodes and tonsils	XLA/XLA GH-/AR agam.
Lymphadenopathy, hepatomegaly, splenomegaly	CVID/HIGM
Severe enteroviral infections, paralytic polio following immunisation, enteroviral meningoencephalitis, enteroviral induced dermatomyositis-like illness	m-heavy chain def. (20%) XLA (10%)
Haematological abnormalities	
Neutropenia	XLA/XLA GH-/AR agam. HIGM1
Lymphopenia	CVID
Thrombocytopenia	CVID
Haemolytic anaemia	CVID
Auto-immunity and rheumatological disorders	
SLE/RA/dermatomyositis/scleroderma	CVID
Arthritis (sterile) GH-/AR agam.	CVID/XLA/XLA
Arthritis, infectious ( <i>Mycoplasma</i> spp and <i>ureoplasma</i> )	XLA/XLA GH-/AR agam. Occasionally CVID
Liver	
Chronic active hepatitis	CVID
Sclerosing cholangitis	HIGM1
Gastrointestinal system	
Diarrhoea (secondary to <i>Giardia lamblia</i> )	XLA/XLA GH-/AR agam./CVID
Diarrhoea (secondary to <i>Cryptosporidium</i> )	HIGM
Nodular lymphoid hyperplasia	CVID
Malabsorption	HIGM/CVID
Granulomas, 'sarcoid-like': lung, liver, kidney	CVID
Malignancy: lymphoid	CVID/HIGM3
Dysmorphic features and skeletal abnormalities	Immuno-osseous dysplasias X-linked anhydrotic ectodermal dysplasia

CVID – common variable hypogammaglobulinaemia; HIGM 1,2,3 – hyper IgM syndromes 1, 2 and 3; XLA – X-linked agammaglobulinaemia; XLA GH- – X-linked agammaglobulinaemia with growth hormone deficiency; AR agam. – autosomal recessive agammaglobulinaemia

'protective' antibody concentration is not the same as a normal immune response. For example, although the protective antitetanus antibody titre is  $\geq 0.1$  IU/ml, most healthy children generate titres at least tenfold higher. In patients who have low, albeit protective, specific antibody levels, it is necessary to evaluate their

response to boosting with a known antigen (e.g. tetanus vaccine) before one can be sure that the immune response is normal. Figure 1 demonstrates the possible responses to boosting with a known vaccine. Tetanus vaccine, a protein antigen, is a very reliable antigen and is recommended for screening patients' ability to make specific antibodies against protein antigens.



Boost with known antigen and follow specific antibody titres at 1, 4 and 6 months post boost.

Fig. 1. Three possible patterns following booster with known antigen in patient who has a low specific antibody level:

- No response to boosting, indicating inability to make a specific antibody response to the antigen in question.
- Normal initial response, but fails to sustain adequate levels, this is an abnormal antibody response.
- Normal initial response and normally sustained antibody levels over the 4-6 months post boost period.

In Figure 1, clearly the responses (a) and (b) represent inability to produce a sustained specific antibody response which therefore implies the presence of an antibody deficiency syndrome. The response (c) is entirely normal.

Testing the response to bacterial polysaccharide antigens is achieved in part by measuring anti-A and anti-B isohaemagglutinins (naturally occurring IgM against a carbohydrate antigen on the surface of enteric *Escherichia coli*) and by assessing the response to polysaccharide vaccines. In either case, responses to these antigens are incomplete and unreliable even in healthy infants younger than 2 years of age; before this age there is no indication to perform these investigations.

The measurement of IgG subclass concentrations needs consideration. The interpretation of IgG subclass concentrations is complicated by the variability of results obtained in different laboratories. Physicians should choose a laboratory that uses appropriately sensitive methodology and has developed its own panel of normal values for each age group. Age has a role in defining the normal concentrations of all IgG subclasses and must be considered in the interpretation of results. In infants under 2 years of age, IgG subclass patterns are highly variable and are not always associated with immunopathology. Interpretation of IgG subclass defects in all patients, but more especially in young children, must be accompanied by an analysis of specific antibody production. The findings should be interpreted by someone experienced in these disorders before committing the patient to life-long, potentially harmful and expensive therapy.

Total circulating IgA concentration is usually measured as a part of an immunoglobulin panel including IgM, IgG, and IgA. Analysis of serum concentrations of IgA subclasses, in addition to total serum IgA, does not contribute to understanding the basis of recurrent infection and is seldom useful. Similarly, measurement of secretory IgA (e.g. in saliva) is usually unnecessary because a deficiency of secretory IgA with a normal serum IgA concentration is rare. Conversely, however,

it is occasionally useful to measure secretory IgA in patients with below-normal serum IgA levels. On the one hand, low serum IgA coupled with low or absent secretory IgA is indicative of pathology, whereas on the other, normal secretory IgA coupled with low serum IgA levels is clearly normal and not indicative of pathology.

Table III outlines the immunopathological characteristics of selected antibody deficiency syndromes.

The evaluation of molecular and genetic defects is performed in specialised laboratories after an immunoglobulin or antibody deficiency has been identified. The description of methods to detect these abnormalities is beyond the scope of this article. When information about a gene defect is obtained for a patient, knowledge of the mutation allows for the identification of carriers and the abnormality in patients and family

Table III. Laboratory features of selected primary antibody deficiency disorders

**X-linked agammaglobulinaemia, X-linked agammaglobulinaemia with growth hormone deficiency, AR agammaglobulinaemia**

- ↓↓ IgG, IgA, IgM, IgE, IgD
- Absent isohaemagglutinins
- Inability to make specific antibodies
- Absence of mature B-lymphocytes
- Normal T-cell function

**Common variable immunodeficiency**

- ↓ IgG, IgA, IgM, IgE, IgD
- Absent isohaemagglutinins
- Inability to make specific antibodies
- Presence of mature B-cells
- T-cell function abnormal in 50% of cases

**Hyper IgM syndromes**

- IgM levels may be normal at diagnosis, but rise with increased antigenic stimulation
- ↓↓ IgG, IgA, IgE, IgD
- Isohaemagglutinins present
- Inability to make specific antibodies
- Presence of mature B-cells
- T-cell function normal

**Impaired polysaccharide responsiveness**

- (selective antibody deficiency)
- Normal IgG, IgA, IgM, IgE, IgD and IgG subclasses
- Normal specific antibody responses to protein antigens
- Absence of specific antibody response to unconjugated pneumococcal or meningococcal vaccination after the age of 2 years
- Presence of circulating B-cells

**Selective IgG subclass deficiencies**

- Variable deficiency of individual or combinations of all four subclasses. Must be followed closely as some evolve into full-blown CVID
- Specific antibody production is normal in the majority

**Antibody deficiency with normal Ig's**

- Normal to increased IgG, IgA, IgM, IgE, IgD
- Absent or unsustained specific antibody titres
- Presence of circulating B-cells

**Transient hypogammaglobulinaemia of infancy**

- ↓ IgG, IgA, IgM
- Variable ability to produce specific antibodies. This improves with time and often precedes normalisation of IgG levels
- Frequently IgG2 and IgG4 subclass deficiency, both normalise with time
- B-cell numbers are normal
- T-cell function normal

members with atypical clinical features and immunological abnormalities. It is therefore useful to secure genetic material from the patient and family members, even when the identification of a genetic abnormality is unavailable. Once a disorder of antibody production is identified further investigations are directed at refining the diagnosis and identifying the molecular defect responsible for the patient's condition – these investigations are usually performed in research laboratories with special interest in various aspects of molecular immunology.

## MANAGEMENT

### General considerations

Patients with humoral immune deficiency require a comprehensive medical approach to their infectious and non-infectious problems. They suffer from acute and chronic infections that need thorough microbiological diagnoses and appropriate antimicrobial therapy. Their inflammatory and rheumatological complications are treated in much the same way that these presentations might be managed in the non-immunodeficient patient.

The importance of good nutrition should be stressed and in patients with significant gastrointestinal pathology, elemental or parenteral therapy may be necessary. Water should be boiled or bottled in circumstances where the water supply may be suspect. Because of the severity of cryptosporidial infections (diarrhoea and sclerosing cholangitis) in patients with HIGM syndromes,<sup>3</sup> it is wise for these patients to boil all drinking water.

Early resection of segmental bronchiectasis is essential in the preservation of long-term pulmonary hygiene.<sup>4</sup> Chronic lung disease that is not amenable to surgery is managed with home physiotherapy and inhalations coupled with regular assessment of pulmonary function and the use of intermittent high-dose courses of antibiotics. This approach is very similar to the management of patients with cystic fibrosis.

One must be aware of the risk of hearing loss in this group of patients and screen hearing frequently.

While it is very important to avoid exposure to potentially infected individuals, it is equally important not to stigmatise or socially isolate children with humoral immune deficiency. As toddlers, however, it is probably advisable to keep these patients out of the daycare environment. Once they are older and particularly when they are on immunoglobulin therapy, affected children are encouraged to participate in normal activities, especially vigorous physical activities.

### Precautions

By definition, patients with antibody deficiency diseases are unable to make specific antibodies; there is therefore no role for active immunisation. Immunisation with live attenuated vaccines is potentially harmful and absolutely contraindicated; a number of patients, especially with XLA, have developed paralytic polio following oral polio vaccine administration.<sup>5</sup> Live polio vaccine is also contraindicated for siblings or other household contacts of patients with immune deficiency because of the high rates of enteric shedding of this virus following immunisation.

Patients suspected of having transient hypogammaglobulinaemia of infancy should be vaccinated according to the normal schedule with the exception of any of the live attenuated vaccines. In this instance, one is able to use responses to inactivated vaccines to predict normalisation of immune function.

### Antibiotics

The most common organisms affecting patients with antibody deficiency are *H. influenzae*, *S. pneumoniae*, *Mycoplasma* spp. and *S. aureus*. When choosing empiric antimicrobial therapy, adequate coverage of the above organisms is essential. Antibiotic dosage and duration of therapy do not differ from that for patients who are immunologically competent. Because patients with antibody deficiency diseases may succumb rapidly to infection, one must institute antibiotic therapy early in the course of illness – it must be recognised that in this group of patients there is an acceptable tendency to overtreat with antibiotics. Treatment of every infection in this group of patients must be directed by accurate microbiological diagnosis; every effort must be made to sample appropriate sites in order to directly identify the infecting organism and its antibiotic susceptibility profile.

*Pneumocystis carinii* pneumonitis prophylaxis using cotrimoxazole (5 mg/kg/dose of trimethoprim 3 x per week) is essential for all patients with HIGM syndrome and certain patients with common variable hypogammaglobulinaemia who demonstrate a significant cellular component to their immune deficiency.

The use of continuous, prophylactic antibiotics should be considered in any patient who continues to experience recurrent infections despite adequate intravenous immunoglobulin replacement therapy. Cotrimoxazole in half therapeutic doses is well tolerated. The use of prophylactic antibiotics is not a substitute for adequate immunoglobulin replacement therapy, nor does it allow for dose reduction of the aforementioned therapy. Prophylactic cotrimoxazole is particularly useful in IgG subclass deficiencies, IgA deficiency and in transient hypogammaglobulinaemia.

### Human immune globulin replacement

Most patients with demonstrated specific antibody deficiency will benefit from intravenous human immunoglobulin replacement therapy. Table IV lists the antibody deficiency conditions in which intravenous immunoglobulin is the mainstay of therapy.

The IgG subclass deficiencies are worthy of more detailed consideration. This group of patients account for the greatest misuse of intravenous immunoglobulin.<sup>6</sup> This therapy is only indicated in the minority of patients with IgG subclass deficiency in whom there

**Table IV. Primary antibody deficiency diseases in which intravenous immunoglobulin replacement therapy is the mainstay of therapy**

- X-linked agammaglobulinaemia
- X-linked agammaglobulinaemia GH
- Autosomal recessive agammaglobulinaemia
- Common variable hypogammaglobulinaemia
- HIGM syndromes
- Immunodeficiency with thymoma (Good syndrome)
- Selective antibody deficiency – patients who experience recurrent infections despite prophylactic antibiotic therapy
- Selective IgM deficiency only if associated with specific antibody deficiency
- Antibody deficiency with normal immunoglobulins
- IgG subclass deficiencies only where there is an associated specific antibody deficiency and the patient experiences recurrent infections despite prophylactic antibiotic therapy.

DATE TIME	EACH ORDER MUST STATE THE PHYSICIANS NAME LEGIBLY	SIGN
	<p>IV IMMUNE GLOBULIN 4% (HUMAN) POLYGAM</p> <div style="border: 1px solid black; padding: 2px; margin-bottom: 10px;">                     LABORATORY: Pre-infusion blood work to be performed prior to each infusion.                 </div> <p>FBC with diff.      IgG, IgA, IgM      AST, ALT                      Other tests as indicated: _____</p> <div style="border: 1px solid black; padding: 2px; margin-bottom: 10px;">                     NURSING                 </div> <ol style="list-style-type: none"> <li>1. Record baseline weight and height</li> <li>2. Record heart rate (HR), respiratory rate (RR), temperature (T) and blood pressure (BP) immediately before infusion and 15, 30 &amp; 60 min after starting infusion; then hourly until 30 minutes after the infusion has ended.</li> <li>3. Anaphylaxis kit bedside (Floor stock). If unavailable, obtain from main Pharmacy.</li> <li>4. Diet as tolerated, activity as tolerated.</li> <li>5. Notify physician if HR &gt;30 beats/min above baseline                          and/or RR &gt;10/min above baseline                          and/or temperature T 1.5oC greater than baseline, if baseline &gt; 38.5oC.                          and/or 1oC greater than baseline if baseline &gt; 38.5oC.                          and/or systolic BP ≥15mmHg above baseline                          and/or diastolic BP ≥10mmHg above baseline                          and/or wheezing, chills, rash, urticaria, pruritis, flushing, myalgias or CNS/behaviour changes noted.</li> </ol> <div style="border: 1px solid black; padding: 2px; margin-bottom: 10px;">                     INFUSION                 </div> <ol style="list-style-type: none"> <li>1. Start IV normal saline _____ mL/h</li> <li>2. Premedicate patients with a history of allergic reactions with Hydrocortisone _____ mg IV (50mg if &lt;30kg, 100mg if &gt;30kg), 15 minutes prior to immune globulin infusion.                      (NOTE: Not given to neonates or bone marrow transplant patients)</li> <li>3. IVIG 4%, _____ Gm ( 0.6 Gm/kg/dose) as a single daily dose x _____ 1 _____ day/s.                      Infuse as follows:                     <ol style="list-style-type: none"> <li>1. Prime the line with immunoglobulin, connect blood filter.</li> <li>2. Start the infusion at:                             <ul style="list-style-type: none"> <li>Increase to _____ ml/h x 15min (1.0 ml/kg/h)</li> <li>increase to _____ ml/h x 15min (2.0 ml/kg/h)</li> <li>increase to _____ ml/h x 15min (4.0 ml/kg/h)</li> <li>increase to _____ ml/h (8.0ml/kg/h) till end of infusion.</li> </ul> </li> <li>3. Observe patient for 20min after the infusion is complete.</li> </ol> </li> </ol> <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div style="width: 30%; border-top: 1px solid black; padding-top: 5px;">Physician Name (print)</div> <div style="width: 30%; border-top: 1px solid black; padding-top: 5px;">Physician Signature</div> <div style="width: 30%; border-top: 1px solid black; padding-top: 5px;">Nurse Signature</div> </div>	

Fig. 2. Sample immunoglobulin order sheet.

has been a proven inability to produce sustained specific antibody levels and who continue to experience recurrent infections even in the face of prophylactic antibiotic therapy.

For practical purposes, in South Africa, human immune globulin for the treatment of primary immune deficiency comes in two forms, the concentrated, 16%, so-called intramuscular form and the 4% intravenous preparation. Studies have demonstrated that maintain-

ing a serum IgG trough level above 5 g/l is associated with reduction in frequency and severity of infection, reduction in hospital admissions and improvement of pulmonary function.<sup>7,8</sup> As adequate trough levels cannot be achieved by intramuscular injections, this modality of therapy should no longer be considered appropriate for patients suffering from primary immune deficiency. The other advantages of intravenous immunoglobulin over intramuscular administration are:

- Ease with which large doses can be given in order to achieve appropriate IgG trough levels
- A more rapid onset of action
- No loss in tissues due to proteolysis
- Avoidance of painful injections.

Pharmacokinetic studies have established that in most patients with humoral immune deficiency, dosing with 400-600 mg/kg every 3 to 4 weeks is sufficient to achieve preinfusion IgG levels of  $\geq 5$  g/l.<sup>8</sup> Dosing must be adjusted to achieve the target IgG trough level – such levels must be measured prior to every infusion.

Intravenous immune globulin must be infused in a clinical setting where the patient is monitored in the same way as for a red cell transfusion. Emergency resuscitation drugs and equipment must be available in the rare event of a severe adverse reaction.<sup>10</sup> The majority of adverse reactions include rigors, mild fever and headaches; these are most frequently related to the rate of infusion of the immune globulin and are diminished when the infusion rate is slowed. Anaphylactic reactions are very rare, but when suspected should result in the immediate cessation of the infusion and institution of appropriate therapeutic measures. Very occasionally, even when infusions are given slowly, certain patients will continue to have symptoms. These patients are the exception rather than the rule and should receive premedication with acetaminophen 15 mg/kg/dose 30 minutes prior to the infusion, and diphenhydramine 1 mg/kg/dose 30 minutes prior to the infusion, both repeated once after 4 hours as necessary.

In patients who have experienced severe reactions, it may be necessary to give hydrocortisone 6 mg/kg/dose 1 hour prior to infusion.<sup>11</sup>

Delayed reactions and headache frequently respond best to treatment/prophylaxis with non-steroidal anti-inflammatories.

It is, however, the author's experience that premedication of any kind is seldom required as long as one pays attention to:

- Proper reconstitution of the immune globulin in order to minimise the formation of aggregates
- Infusion of the immune globulin through a normal blood filter
- Slow and gradually increasing infusion rates.

A sample order sheet for the management of an intravenous immunoglobulin infusion is demonstrated in Figure 2. This reflects the author's practice and may not comply with infusion rates recommended by all manufacturers of intravenous immunoglobulin. Prior to infusing immunoglobulin it is essential that the clinician contact the manufacturer or consult the manufacturer's guidelines for infusion details.

Subcutaneous immune globulin infusions using the 16%, so-called intramuscular immune globulin products have been in use for a number of years.<sup>11-14</sup> By fractionating the total monthly immune globulin dose (400-600 mg/kg/dose), into 3-4 subcutaneous infusions per week, one is able to deliver the total monthly dose in small aliquots and achieve adequate IgG steady state levels. This method requires considerable commitment on the part of the patient and a well-structured training and support system provided by the caregiver. Subcutaneous therapy should not be initiated by inexperienced clinicians and is mentioned here for completeness sake.

## FUTURE DIRECTIONS

The future for cure of many antibody deficiency disorders is bright. Gene therapy programmes for a number of immune deficiency diseases are in existence.<sup>15,16</sup>

Candidate disorders for gene therapy are X-linked agammaglobulinaemia and the hyper IgM syndromes. These future directions reinforce the notion that in addition to the clinical diagnosis of antibody deficiency, identification of the molecular defect is equally important.

## RESOURCES

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Primary Immunodeficiency Network of South Africa (PiNSA), [www.pinsa.org.za](http://www.pinsa.org.za)

Immune Deficiency Foundation, [www.primaryimmune.org](http://www.primaryimmune.org)

The Jeffery Modell Foundation, [www.jmfworld.com](http://www.jmfworld.com)

Primary Immunodeficiency Association (UK), [www.pia.org.uk](http://www.pia.org.uk)

International Patient Organisation for Primary Immunodeficiencies (IPOPI), [www.ipopi.org](http://www.ipopi.org)

European Society for Immunodeficiency (ESID), [www.esid.org](http://www.esid.org)

National Bioproducts Institute (Manufacturer of human immunoglobulin in South Africa), [www.nbi-kzn.org.za](http://www.nbi-kzn.org.za)

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