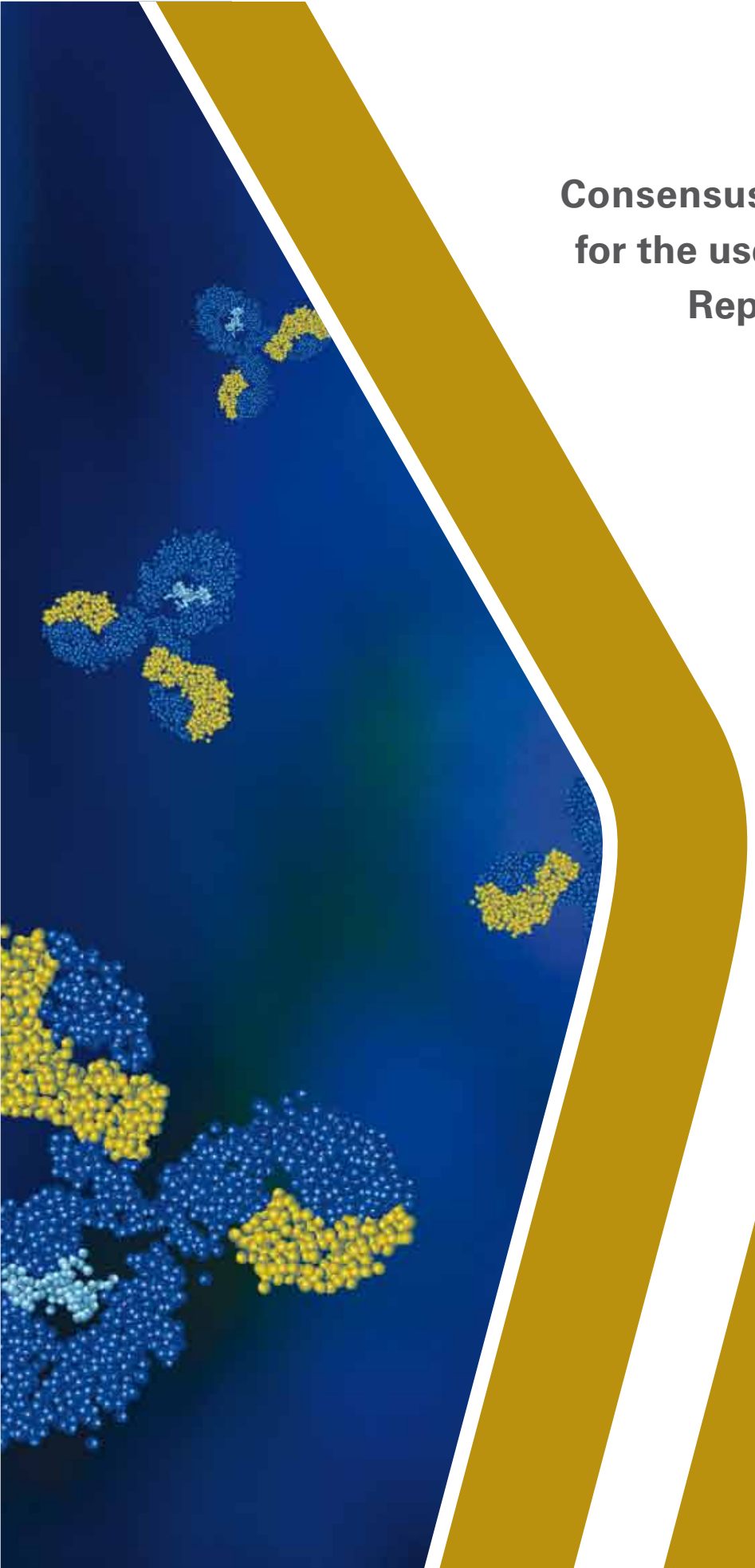
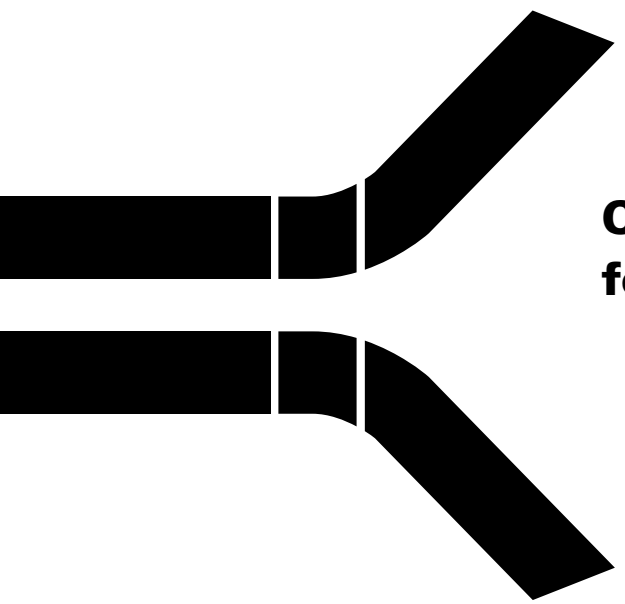


Consensus Recommendations for the use of Immunoglobulin Replacement Therapy in Immune Deficiency

APIIEG

Asia Pacific Immunoglobulins In Immunology Expert Group

2nd Edition, July 2009



Consensus Recommendations for the use of Immunoglobulin Replacement Therapy in Immune Deficiency

2nd Edition, July 2009

ISBN 978-0-9806702-0-2

This publication has been made possible by an unrestricted educational grant from CSL Bioplasma.

Table of Contents

Foreword

Consensus recommendations for the use of immunoglobulin replacement therapy in immune deficiency

Asia Pacific Immunoglobulins in Immunology Expert Group Inc (APIIEG)

Antibody deficiency is the most common class of immune deficiency in children and adults. Delayed diagnosis can result in preventable complications such as life-threatening bacterial infections and bronchiectasis. Where available, immunoglobulin replacement therapy is the treatment of choice for primary antibody deficiency syndromes to prevent recurrent infections and irreversible organ damage. Immunoglobulin replacement therapy has also been used to prevent infection in secondary immune deficiencies as well as to support bone marrow transplantation.

More recently, the use of plasma derived immunoglobulin products has expanded into immunomodulatory therapy for the treatment of a growing number of immune mediated conditions, and uptake of immunoglobulin products has increased significantly. This has resulted in increased demand for immunoglobulin products and highlighted the need to develop clinical guidelines to support optimal use of these products in the treatment of immune disorders. Whilst guidelines on the indications for immunoglobulin therapy have been produced across the globe, no specific document existed in the Asia Pacific region to provide guidance for immunologists and other clinicians on the approach to immunoglobulin replacement therapy for immune disorders in clinical practice.

In recognition of the growing economic and educational cooperation between Asia Pacific countries, the Asia Pacific Immunoglobulins in Immunology Expert Group (APIIEG) was formed to develop consensus recommendations for the use of immunoglobulin products in immune disorders in the region. The first objective was to develop consensus recommendations regarding immunoglobulin replacement therapy in immune deficiency. The members of APIIEG were invited to take part in this endeavour due to their specific knowledge and experience with immunoglobulin replacement therapy for immune deficiencies and their willingness to devote significant time to the process. The first meeting of the group took place in October 2006. By February 2008, the group established itself as an incorporated association. Following 17 months of vigorous debate, the consensus recommendations were finalised and ratified by the group in April 2008. During the development of the recommendations, APIIEG sought comment from the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) and the Australasian Society of Clinical Immunology and Allergy (ASCIA), and I am proud to say that the final document has been endorsed by APAAACI and reviewed by ASCIA.

The aim of the *Consensus Recommendations for the Use of Immunoglobulin Replacement Therapy in Immune Deficiency* is to support immunologists and other clinicians in their use of immunoglobulin products in clinical practice. The consensus document provides practical recommendations on: evaluation of humoral immune responses in patients, when to consider the diagnosis of antibody deficiency, indications for immunoglobulin replacement therapy in primary as well as secondary

antibody deficiency and appropriate administration and monitoring of immunoglobulin replacement therapy. A discussion of adverse effects associated with immunoglobulin replacement therapy is also presented.

These consensus recommendations have been produced from evidence based literature and expert opinion. As knowledge about and experience with immunoglobulin replacement therapy increase, revision of clinical practice will be required. It is the intention of the authors to update these recommendations annually, or as the need arises. This second edition, published in July 2009, contains minor editorial amendments to the text published in the first edition in June 2008, and is available from the Group's website: www.apiieg.org

In addition to creating the consensus recommendations, the 'Statement of Purpose' of the Asia Pacific Immunoglobulins in Immunology Expert Group is to organise symposia and conventions on the subject of immunoglobulins and their use in immune disorders. The launch of edition 1 of these consensus statements at the 13th International Congress on Infectious Diseases in June 2008 in Kuala Lumpur, Malaysia, and at the 19th ASCIA Annual Scientific Meeting in Melbourne, Australia on November 2009, were the first of many activities to inform clinicians in the region.

Finally, consensus recommendation documents are significant undertakings and I would like to thank all the members of the group for their dedication and hard work. I would like to extend a special thank you to our families for supporting us during the creation of this document, which often involved time away from home and additional commitments on top of our already busy schedules.

A/Prof Mimi Tang

Chair, Asia Pacific Immunoglobulins in Immunology Expert Group Inc.

July 2009

Endorsement

Message from the President of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) on

Consensus Recommendations for the Use of Immunoglobulin Replacement Therapy in Immune Deficiency – 2008

As published by Asia Pacific Immunoglobulins in Immunology Expert Group Inc (APIIEG)

June 9, 2008

It is a great pleasure for me to write a foreword for the timely recommendations for the use of immunoglobulin replacement therapy in immune deficiency in the Asia Pacific.

The region is the world's most populated area with over 4 billion residents (over 60% of the world population). Certainly, a large number of patients with immune deficiency, particularly with B cell defects, exist in this region of the world. Treatment of patients with such disorders has been problematic throughout the Asia Pacific, not only because of lack of IVIg but also because of difficulty in arriving at a correct diagnosis.

These *Consensus Recommendations* not only provide information on IVIg treatment but also contain significant recent information on appropriate diagnosis of diseases due to B cell defects. These *Consensus Recommendations* represent a mini-primer for B cells defects for those who are interested in the diagnosis and treatment of primary immunodeficiencies, particularly for immunologists and physicians who care for such patients in the region.

On behalf of the Asia Pacific Association of Allergy, Asthma and Immunology (APAAACI), I would like to congratulate the Asia Pacific Immunoglobulins in Immunology Expert Group Inc (APIIEG), particularly Associate Professor Mimi Tang, for taking up such a formidable task. I would also like to thank Associate Professors, Orathai Piboonpocanun and Voravich Luagnwedchakarn (Faculty of Medicine Siriraj Hospital, Mahidol University), Pantipa Chatchatree (Faculty of Medicine, Chulalongkorn Hospital) and Lynette Pei-Chi Shek (Faculty of Medicine, National University of Singapore) for agreeing to review this document.

APAAACI, in endorsing this document, wish that these *Consensus Recommendations* will be the beginning of continuing efforts that will lead to an improvement of care of such patients in the region. Efforts to increase availability of IVIg and to make such treatment affordable in the region are highly recommended.

Professor Pakit Vichyanond, MD
Faculty of Medicine Siriraj Hospital,
Bangkok Thailand

President, Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI)

These guidelines have been reviewed by the Australasian Society of Clinical Immunology and Allergy (ASCIA). ASCIA is the peak professional body of Clinical Immunologists and Allergists in Australia and New Zealand. Website: www.allergy.org.au

Chapter 1

When to consider a diagnosis of antibody deficiency

- The hallmark clinical presentation is infection
- The type of infection provides a clue to the underlying immune defect and condition
- Antibody deficiency is the most common class of immune deficiency
- Antibody deficiency may be a feature of either a primary or secondary immune disorder
- Diagnosis may often be delayed and result in preventable complications

There are more than 150 primary immunodeficiency syndromes (PIDs) described[1] as well as a range of secondary immune deficiency states. The PIDs have been classified into combined B and T cell deficiencies and predominantly antibody deficiencies (see Table 1 A and B), and other well defined immunodeficiency syndromes. The hallmark presenting feature is infection. Immunoglobulin replacement is the mainstay of therapy for the predominantly antibody deficiencies, but it is also an important therapeutic modality in combined T and B cell immune deficiency syndromes.

Antibody deficiency disorders constitute a group of heterogenous disorders ranging from inherited PIDs to acquired disorders of immune defense (see chapters 3-6). The early diagnosis of PID requires a high index of suspicion as the presentation is usually nonspecific. A delay in diagnosis has adverse effects on the clinical outcome, as it can result in irreversible damage to affected organs such as bronchiectasis and chronic lung disease, and in some cases, even death.

Antibody deficiency should always be considered in patients presenting with severe, unusual, frequent or recurrent infections. The most common clinical manifestations are bacterial infections of the sinuses, ears and lungs, but other features may be more subtle (see below). Unfortunately, underlying immune defects are commonly overlooked, and delays in diagnosis and treatment may lead to detrimental effects on outcome, as early treatment is paramount in preventing long term complications. The presenting clinical manifestations depend largely on the type and severity of the underlying immune defect. Children may present with failure to thrive and adults with weight loss. In patients with milder phenotypes, the clinical examination may be entirely negative. Warning signs of a possible underlying immunodeficiency disorder have been developed by the National Primary Immunodeficiency Resource Centre (http://www.info4pi.org/index.cfm?CFID=4441749&CFTOKEN=89405863)[2] and the European Society of Immunodeficiencies.[3] A list of clinical presentations which may suggest an underlying immunodeficiency has been adapted from these resources and is shown in Table 2. This list is not exhaustive, but aims to provide practising clinicians with an awareness of when to consider immunodeficiency in their patients. Modifications of this list may be considered by the respective specialists to tailor to regional differences.

Age of presentation

The age of onset of symptoms in severe antibody disorders such as X linked agammaglobulinaemia (XLA) is typically in the second six months of life when passively acquired maternal antibodies have diminished. However, the diagnosis is often made much later. In a large US series of XLA, the mean age of diagnosis was 5.4 years, although it may be earlier in those with a positive family history (2.6 years).[4] Common variable immunodeficiency disorders (CVIDs) on the other hand tend to present beyond the first five years of life and often into adulthood, due to a later onset of symptoms.[5] It should be noted that the phenotype of these immunodeficiency syndromes is known to be highly variable. For example, XLA may present with first symptoms in adulthood,[6] when CVIDs and acquired antibody deficiencies are usually identified. This emphasises the point that PIDs do not only present in childhood and must also be considered in adults[7, 8] when acquired (late onset) immunodeficiency disorders are more common. Reaching a diagnosis in adult patients is as important as it is in children, as an early diagnosis is critical for a favourable outcome.

Infections

An increased susceptibility to infection is the hallmark of immunodeficiency disorders, including antibody deficiency. In particular, infections that are severe, recurrent, unusual or chronic and require frequent courses of antibiotic therapy or result in organ damage and dysfunction, should alert the clinician to a possible underlying immunodeficiency syndrome. Primary immune deficiency should be considered following a single severe infection. Adult patients are often only diagnosed after many years of recurrent infection by which time they have developed complications such as bronchiectasis, so early suspicion of immune deficiency is important.

Pyogenic sinopulmonary infection, including otitis media, is common in patients with antibody deficiency disorders, and the incriminating infective organisms are often the encapsulated bacteria; namely *Streptococcus pneumoniae* and *Haemophilus influenzae*. However, infections due to several other bacteria such as *Staphylococcus* spp, *Pseudomonas* spp, and Salmonella, are also well documented. Persistence of these infections often results in sequalae such as bronchiectasis and mastoiditis, and therefore these complications are important indicators for evaluating antibody function to exclude antibody deficiency disorders. In those with severe antibody deficiency, bacteraemia and sepsis involving the encapsulated bacteria is not uncommon, with case reports of other unusual bacteria such as *Campylobacter lari* [9] and *Helicobacter cinaedi*.[10]

In the absence of obvious antibody deficiency, recurrent otitis media and chronic otorrhoea may also be a manifestation of specific antibody deficiency (defined as poor serological response to polysaccharide antigens but normal levels of immunoglobulins and IgG subclasses, and normal responses to protein antigens [11, 12] (Refer to Chapter 4).

Persistent or chronic diarrhoea may be a feature of antibody deficiency. The ensuing malabsorption results in failure to thrive in children and significant weight loss in adults. In a series of cases with XLA and common variable immunodeficiency disorders, these gastrointestinal manifestations were related to wide ranging aetiologies including parasitic infestation such as giardiasis, small bowel lymphoma, inflammatory bowel disease and non-specific villous atropy.[13,14]

Viruses. In general, patients with antibody deficiency do not experience severe viral infections. An exception is where there is an associated T cell defect (eg Epstein Barr virus infections in X-linked lymphoproliferative disease, or respiratory syncitial virus in severe combined immunodeficiency). In patients with isolated antibody deficiency such as XLA, enteroviral infections may be complicated by a persistent meningoencephalitis and may be associated with a dermatomyositis-like illness.[15,16,17] Additionally, vaccine associated poliomyelitis can result from chronic infection after vaccination with live attenuated polioviruses (oral Sabin).[18-20] These infections may be related to chronic infection of the gut by vaccine-derived poliovirus and patients may continue to excrete large amounts of virus for years.[21]

Chronic arthritis may be a manifestation of hypogammaglobulinaemia, and may be the presenting problem. Monoarthritis or oligoarthritis is the usual pattern. Besides bacterial infections, infections with echoviruses, coxsackieviruses, adenoviruses,[4] and *Ureaplasma urealyticum* [22] have been identified in the joint fluid of these patients. In some cases however, the arthritis may have no

demonstrable relation to chronic infection and may therefore be a manifestation of autoimmunity.[23,24.]

Opportunistic infections occur as a result of immunodeficiencies associated with innate, T cell or severe combined B and T cell defects (eg severe combined immunodeficiency (SCID)) rather than in predominantly antibody immunodeficiencies. Those with SCID have profound defects in cell mediated immunity and may present in early infancy with persistent infections with *Candida albicans*, *Pneumocystis jiroveci (carinii) pneumonia, cytomegalovirus*, Epstein Barr virus, and vaccination with Bacillus Calmette-Guerin infection can result in dissemination. The persistence and severity of these infections almost invariably results in failure to thrive. Gram positive and gram negative sepsis are common manifestations. Common childhood infections such as varicella-zoster virus, adenovirus and other respiratory viruses may be acute and life threatening in these children. Infants with SCID also lack the ability to reject allografts, leaving them at risk for graft versus host disease, either from T cell depleted haploidentical parental transplants or persistence of maternal cells, for which an eczematous rash, splenomegaly and eosinophilia are common manifestations.[25]

Haematological manifestations

The most common are the cytopaenias, which are most often autoimmune in aetiology.

Thrombocytopenia, particularly immune thrombocytopaenic purpura, autoimmune haemolytic anaemia, neutropenia, lymphopaenia and splenomegaly can occur, particularly in CVIDs.[26] Other primary immunodeficiency conditions also have specific cytopaenias such as hyper IgM syndrome and Wiskott-Aldrich Syndrome.

A wide range of autoimmune disorders from systemic autoimmunity such as systemic lupus erythematosus to more organ-specific disorders such as inflammatory bowel disease and pernicious anaemia have also been described in PID. Arthritis may be the presenting problem, particularly in CVIDs, and is more often septic or aseptic than autoimmune. However, arthritis mimicking rheumatoid arthritis has also been described in CVIDs.[27]

Granulomatous diseases

Although not confined to CVIDs, the development of granulomatous inflammation with sarcoid-like lesions has been well described in this condition.[28,29] The involvement of lung and liver worsens the prognosis and is often difficult to treat.[30] In CVIDs, an association of human herpes virus 8 infections with granulomatous lymphocytic interstitial lung disease has been postulated to increase the risk of developing lymphoma.[31] Sclerosing cholangitis is a well described consequence of hyper IgM syndrome.

Malignancies

Some malignancies and or their treatment may result in a secondary antibody deficiency (eg chronic lymphocytic leukemia, thymoma, multiple myeloma, non-hodgkins lymphoma). There is also an increased risk of malignancy in the primary antibody deficiency disorders, however this is usually not a presenting feature.[29]

Familial Inheritance

In conditions associated with severe immune defects, a family history of unexplained mortality in a sibling or relative may be of significance and in X-linked disorders such as SCID, male mortality should raise a suspicion. Specific inheritance patterns such as X-linked inheritance as seen in XLA and hyper IgM syndrome are also important to note. The presence of parental consanguinity should alert one to the possibility of autosomal recessive conditions such as autosomal recessive agammaglobulinaemia. Commonly however, disease is sporadic and in that case there is no family history of immune deficiency.

Table 1

Classification of Primary Immunodeficiency Disorders
A: Combined T cell and B cell immunodeficiencies

Circulating T cells	**Circulating B**	**Serum immunoglobulin**	**Disease**
Markedly decreased	Normal or increased	Decreased	T^-B^+ SCID*
Markedly decreased	Decreased or normal	Decreased	T^-B^- SCID*
Present	Normal or decreased	Decreased, except increased IgE	Omenn syndrome
Normal	IgM^+ and IgD^+ B cells present, but others absent	IgM increased or normal, other isotypes decreased	CD40 ligand deficiency
Normal	IgM^+ and IgD^+ B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	CD40 deficiency
Progressive decrease	Normal	Normal or decreased	PNP* deficiency
Decreased CD8, normal CD4 cells	Normal	Normal	MHC* class I deficiency
Normal number, decreased CD4 cells	Normal	Normal or decreased	MHC* class II deficiency

B: Predominantly antibody deficiencies

Serum immunoglobulin	**Circulating B cells**	**Disease**
Severe reduction in all serum immunoglobulin isotypes	Profoundly decreased or absent	Btk deficiency* μ Heavy chain deficiency λ5 Deficiency Igα deficiency Igβ deficiency BLNK deficiency* Thymoma with immunodeficiency Myelodysplasia
Severe reduction in serum IgG and IgA (Low IgG and IgA; variable IgM)	Normal, low or very low numbers	Common variable immunodeficiency ICOS deficiency CD19 deficiency X-linked lymphoproliferative syndrome
Severe reduction in serum IgG and IgA with normal/elevated IgM	Normal numbers	CD40L deficiency CD40 deficiency Activation-induced cytidine deaminase deficiency UNG deficiency
Isotype or light chain deficiencies with (One or more IgG and/or IgA subclasses as well as IgE may be absent)	Normal numbers	Ig heavy chain deletions # χ chain deficiency Isolated IgG subclass deficiency IgA deficiency associated with IgG subclass deficiency Selective IgA deficiency
Normal IgG A and M	Normal numbers	Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells
IgG and IgA decreased	Normal numbers	Transient hypogammaglobulinemia of infancy with normal numbers of B cells

Adapted from Geha RS, et al. International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol. 2007 Oct;120:776-94

*SCID Severe combined immunodeficiency; PNP purine nucleoside phosphorylase;
MHC major histocompatilibity complex; btk Bruton tyrosine kinase; BLNK B cell linker protein;
ICOS inducible costimulator; UNG uracyl DNA glycosylase.

these conditions are not necessarily clinically significant as they are not associated with recurrent infections

Table 2:
Signs which may indicate Immunodeficiency

Medical History

- Frequent middle ear infections (>8 per year)
- Middle ear infection associated with a persistent purulent discharge
- Recurrent serious sinus infections
- Severe infections (eg. meningitis, osteomyelitis, pneumonia) requiring IV antibiotics
- Persistent production of purulent sputum
- Infections in unusual areas eg. perianal area
- Recurrent deep skin or organ abscesses
- Infections with unusual or opportunistic organisms
- Persistent diarrhoea
- Family history of primary immunodeficiency

Clinical Features

- Poor growth, failure to thrive in children, or weight loss in adults
- Absent lymph nodes or tonsils
- Persistent unexplained oral thrush after one year of age

Other Features (more common in adult patients)

- Autoimmune cytopaenias
- Granuloma formation at any site (often misdiagnosed as sarcoidosis)
- Gluten insensitive enteropathy
- Unexplained hepatomegaly especially in adults
- Unexplained splenomegaly in children or adults
- Lymphoid interstitial pneumonitis

*Adapted from the '10 warning signs of immunodeficiency' developed by the National Primary Resource Foundation (http://www.info4pi.org/index.cfm?CFID=4441749&CFTOKEN=89405863) and the European Society of Immunodeficiency Diseases[3]. Note: The specificity and sensitivity of these criteria for the detection of PID have not been formally assessed in population studies.

References

1. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120(4):776-94.

2. Information from your family doctor. Warning signs of primary immunodeficiency. Am Fam Physician 2003;68(10):2011.

3. de Vries E. Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol 2006;145(2):204-14.

4. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 2006;85(4):193-202.

5. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes Blood 2008;112(2):277-86

6. Mitsui T, Tsukamoto N, Kanegane H, Agematsu K, Sekigami T, Irisawa H, et al. X-linked agammaglobulinemia diagnosed in adulthood: a case report. Int J Hematol 2006;84(2):154-7.

7. Mansouri D, Adimi P, Mirsaedi M, Mansouri N, Tabarsi P, Amiri M, et al. Primary immune deficiencies presenting in adults: seven years of experience from Iran. J Clin Immunol 2005;25(4):385-91.

8. Riminton D S and Limaye S. Primary immunodeficiency diseases in adulthood. Intern Med J 2004;34(6):348-54.

9. Jirapongsananuruk O, Wanotayan K, Phongsamart W, Chokephaibulkit K, Visitsunthorn N, Luangwedchakarn V, et al. Recurrent Campylobacter lari bacteremia in X-linked agammaglobulinemia: a case report and review. Asia Pacific J Allergy Immunol 2006;24(2-3):171-4.

10. Simons E, Spacek LA, Lederman HM and Winkelstein JA. Helicobacter cinaedi bacteremia presenting as macules in an afebrile patient with X-linked agammaglobulinemia. Infection 2004;32(6):367-8.

11. Ambrosino DM, Siber GR, Chilmonczyk BA, Jernberg JB and Finberg RW. An immunodeficiency characterized by impaired antibody responses to polysaccharides. N Engl J Med 1987;316(13):790-3.

12. Boyle RJ, Le C, Balloch A and Tang ML. The clinical syndrome of specific antibody deficiency in children. Clin Exp Immunol 2006;146(3):486-92.

13. Washington K, Stenzel TT, Buckley RH and Gottfried MR. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Pathol 1996;20(10):1240-52.

14. Teahon K, Webster AD, Price AB, Weston J and Bjarnason I. Studies on the enteropathy associated with primary hypogammaglobulinaemia. Gut 1994;35(9):1244-9.

15. Wilfert CM, Buckley RH, Mohanakumar T, Griffith JF, Katz SL, Whisnant JK, et al. Persistent and fatal central-nervous-system ECHOvirus infections in patients with agammaglobulinemia. N Engl J Med 1977;296(26):1485-9.

16. Rudge P, Webster AD, Revesz T, Warner T, Espanol T, Cunningham-Rundles C, et al. Encephalomyelitis in primary hypogammaglobulinaemia. Brain 1996;119:1-15.

17. Katamura K, Hattori H, Kunishima T, Kanegane H, Miyawaki T and Nakahata T. Non-progressive viral myelitis in X-linked agammaglobulinemia. Brain Dev 2002;24(2):109-11.

18. Buckley RH. Primary immunodeficiency diseases due to defects in lymphocytes. N Engl J Med 2000;343(18):1313-24.

19. Wright PF, Hatch MH, Kasselberg AG, Lowry SP, Wadlington WB and Karzon DT. Vaccine-associated poliomyelitis in a child with sex-linked agammaglobulinemia. J Pediatr 1977;91(3):408-12.

20. Sankano T, Kittaka E, Tanaka Y, Yamaoka H, Kobayashi Y and Usui T. Vaccine-associated poliomyelitis in an infant with agammaglobulinemia. Acta Paediatr Scand 1980;69(4):549-51.

21. Labadie K, Pelletier I, Saulnier A, Martin J and Colbere-Garapin F. Poliovirus mutants excreted by a chronically infected hypogammaglobulinemic patient establish persistent infections in human intestinal cells. Virology 2004;318(1):66-78.

22. Mohiuddin AA, Corren J, Harbeck RJ, Teague JL, Volz M and Gelfand EW. Ureaplasma urealyticum chronic osteomyelitis in a patient with hypogammaglobulinemia. J Allergy Clin Immunol 1991;87(1 Pt 1):104-7.

23. Sordet C, Cantagrel A, Schaeverbeke T and Sibilia J. Bone and joint disease associated with primary immune deficiencies. Joint Bone Spine 2005;72(6):503-14.

24. Verbruggen G, De Backer S, Deforce D, Demetter P, Cuvelier C, Veys E, et al. X linked agammaglobulinaemia and rheumatoid arthritis Ann Rheum Dis 2005;64(7):1075-8.

25. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, et al. Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 1997;130(3):378-87.

26. Arkwright PD, Abinun M and Cant AJ. Autoimmunity in human primary immunodeficiency diseases. Blood 2002;99(8):2694-702.

27. Swierkot J, Lewandowicz-Uszynska A, A. Chlebicki A, Szmyrka-Kaczmarek M, Polanska B, Jankowski A, et al. Rheumatoid arthritis in a patient with common variable immunodeficiency: difficulty in diagnosis and therapy. Clin Rheumatol 2006;25(1):92-4.

28. Cunningham-Rundles C and Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92(1):34-48.

29. Mechanic LJ, Dikman S and Cunning ham-Rundles C. Granulomatous disease in common variable immunodeficiency. Ann Intern Med 1997;127(8 Pt 1):613-7.

30. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK and Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol 2004;114(2):415-21.

31. Wheat WH, Cool CD, Morimoto Y, Rai PR, Kirkpatrick CH, Lindenbaum BA, et al. Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. J Exp Med 2005;202(4):479-84.

Chapter 2

Evaluation of humoral immune function to guide the need for immunoglobulin replacement

- Evaluation of immune function must be performed in the context of age-specific reference ranges that are specific for the population and laboratory method being used
- Hypogammaglobulinaemia is not a diagnosis and requires further assessment
- Some antibody deficiencies may evolve with time and repeat evaluation of antibody function may be required
- The evaluation of humoral immune function is guided by the clinical setting and may be performed in a staged approach
- Anti-pneumococcal antibodies are only measured in specialized laboratories and their interpretation is complex
- The finding of isolated low IgG subclass levels may not be clinically significant

This chapter will focus on the evaluation of humoral immunity, which can guide the need for immunoglobulin (Ig) replacement. It will not elaborate on investigations to assess T cell, natural killer (NK) cell, phagocytic and complement functions.

When a primary immunodeficiency is suspected, the clinical presentation will guide the planning of investigations.[1] Investigation of humoral immune function may be undertaken in a staged approach (Table 1). Alternatively, if there is a high index of suspicion for a primary immune deficiency, stages 1-4 may be undertaken together. First line investigations for patients suspected of having an antibody deficiency include a full blood count (FBC) and serum Ig (IgG, IgA, IgM and IgE) measurements. More detailed evaluation of humoral immune function can be pursued based upon the results of these first line tests and the clinical presentation. The first line tests will also provide helpful information on the likelihood of other primary immune deficiencies.[2] Immunoglobulin levels and lymphocyte counts vary significantly with age and interpretation of laboratory results must be made in the context of age, population, and laboratory method specific ranges.[3] For example, age related changes in immunoglobulin levels are shown in Figure 1. Local laboratories should be encouraged to develop age specific reference ranges relevant to the local population. Interpretation of results for children using adult reference ranges is a common error.

Table 1
Staged investigations of humoral immunodeficiency

1	Full blood count and serum immunoglobulin IgG, IgA, IgM, IgE
2	Serum, urinary and faecal proteins
3	Lymphocyte markers: CD3 with CD4 [T helper cells], CD3 with CD8 [T cytotoxic cells], CD16 with CD56 [NK cells], CD19 or CD20 [B cells]
4	Antigen specific antibody response and IgG subclasses
5	More detailed B cell immunophenotyping such as switched memory B cells CD27 with surface IgM
6	Specific genetic testing

Stage 1

a) FBC

Lymphocyte counts should be interpreted using age appropriate normal ranges. A low lymphocyte count (less than 2000 cells/μl) in a newborn or an infant with recurrent and/or persistent infections will require urgent investigation to exclude severe combined immunodeficiency (SCID) although a normal lymphocyte count does not exclude this diagnosis. An elevated lymphocyte count in adults raises the possibility of chronic lymphocytic leukaemia, and further evaluation of B cell phenotype is required. A low neutrophil count can be associated with X-linked agammaglobulinaemia (XLA), X-linked hyper-IgM syndrome, common variable immunodeficiency disorders (CVIDs) and Wiskott Aldrich syndrome (WAS). Hemolytic anaemia and thrombocytopenia can occur in IgA deficiency, CVIDs, and some forms of hyper-IgM immunodeficiency. A low platelet count with small platelet volume is highly suggestive of WAS in a boy with eczema and recurrent infection. X-linked thrombocytopenia, allelic with WAS, is also characterized by small platelets.

b) Serum immunoglobulins (IgG, IgA, IgM, IgE)

IgG is the only isotype that crosses the placenta during pregnancy, and serum IgG levels in the first few months of life largely represent maternal IgG. This is gradually replaced by the infant's IgG and by 10 to 12 months of age, the IgG is nearly entirely the infant's. Premature infants have lower levels of IgG at birth than term infants, and levels reach a nadir at 3 months of age. IgA may not be detectable in the first 6 months of life. Failure to detect IgA in infancy may not necessarily indicate IgA deficiency.

Hypogammaglobulinaemia is not necessarily indicative of an immune deficiency and always requires further clinical and laboratory assessments for an underlying cause. Conversely, borderline IgG levels, for example 4 to 6 g/L, or normal IgG levels do not necessarily exclude humoral immunodeficiencies, such as CVID, specific antibody deficiency, or IgG subclass deficiency, and additional testing of functional antibody responses is required. The value of IgG subclass measurements is uncertain (see Chapter 4). In hyper-IgM syndrome, levels of IgG and IgA are low, while IgM may be normal (early in disease) or elevated (usually later in disease). An isolated absence of IgA (<0.05g/l) is reported to occur in up to 1:500 people in Caucasians, and is usually not associated with an increased risk of infections. High serum IgE levels in a clinical context of recurrent cold abscesses due to *Staphylococcus aureus* may suggest a diagnosis of hyper-IgE syndrome, although elevated IgE is most commonly observed with atopic disorders such as atopic dermatitis, and is also seen with systemic helminth infections. Reduced serum immunoglobulin levels are also seen with the cellular immune deficiencies (Chapter 5).

Stage 2

Serum, urinary and faecal proteins

Other causes of low Ig levels include multiple myeloma, protein-losing enteropathy and nephrotic syndrome.

Serum and urinary protein electrophoresis should be performed in adults with reduced levels of IgG or IgM to exclude the presence of a paraprotein. Multiple myeloma is a common reason for failure of polyclonal antibody production. Estimation of polyclonal immunoglobulin levels may be affected by the presence of monoclonal paraproteins.

Serum albumin and total protein should be performed in all patients, to exclude a protein-losing state. Urinary albumin and protein may be performed to assess for renal loss. Faecal clearance of alpha$_1$-antitrypsin or ^{51}Cr-labelled albumin can be performed to assess for gastrointestinal loss.

Stage 3

Lymphocyte markers

If antibody deficiency is demonstrated, enumeration of lymphocyte subsets should be considered (Figure 2). Lymphocyte markers of interest include CD19 and/or CD20 for B cells; CD3, CD4 and CD8 for T cells; and CD16 and/or CD56 for NK cells.

Panhypogammaglobulinaemia (low or no IgG, A and M) with low or no B cells will suggest X-linked (XL) or autosomal recessive (AR) agammaglobulinaemia. CVIDs is a diagnosis of exclusion and other diagnoses including XLA, X-linked lymphoproliferative syndrome (XLP) and hyper-IgM syndromes must be excluded.[4] Low B and/or T cell numbers or a reversed CD4:CD8 ratio may be seen in some cases of CVIDs.

Very low T cell numbers with or without low NK cell numbers will suggest cellular immune deficiencies such as SCID or combined immunodeficiency (CID). In many of these conditions B cell number is also reduced (See Chapter 2, Figure 2).

Stage 4

a) Antigen specific antibody responses

Assessment of antigen-specific antibody responses should be considered as part of the evaluation of patients with mild to moderate reductions in serum IgG. Evaluation of specific antibody responses is unlikely to provide additional information in patients with markedly reduced IgG levels and/or absent B cells.

In patients with normal serum IgG, IgA and IgM levels, and normal B and T cell subsets, in whom there is strong suspicion of humoral immunodeficiency based on clinical presentation, further investigation of functional antibody responses to protein and polysaccharide antigens should be pursued. Evaluation of IgG subclass levels may also be considered (see Chapter 4).

Isohaemagglutinin titres against blood group A and B antigens, which can be detected in most normal children beyond the first 6 months of life except those with blood group AB, provide information on antigen specific IgM responses.[5] By the age of three years, 98% of patients with blood groups A, B, or O have isohaemagglutinins with a titer of at least 1:16.[6] Low or absent isohaemagglutinin titres in a patient without type AB blood group is indicative of a poor functional IgM response, and may be seen in antibody deficiency syndromes. However, isohaemagglutinin titres may often be normal at the time of diagnosis of antibody deficiency syndromes such as CVIDs, and wane over time.

Measurement of specific IgG titres against commonly used protein antigen vaccines, such as tetanus and diphtheria toxoid, hepatitis A and B and rubella, can provide information on functional IgG responses to protein antigens. If titres are reduced, booster vaccinations may be administered and antigen specific IgG titres re-evaluated four weeks after immunization. Anti-streptolysin O titre (ASOT) may also be helpful as most individuals have had prior exposure. Absence of specific IgG to measles, mumps or chicken pox in the presence of known history of infection is useful as this indicates failure of specific antibody synthesis.

Evaluation of specific IgG titres against polysaccharide antigens is also required in the assessment of functional antibody responses. The pneumococcal vaccine, Pneumovax®, remains the only readily available unconjugated polysaccharide vaccine and is used to evaluate functional IgG responses to polysaccharide antigens. Prevenar® contains polysaccharide antigens conjugated to a protein, and therefore does not specifically assess the antibody response to polysaccharide antigen alone (See Chapter 4). Criteria for interpretation of specific antibody responses to polysaccharide antigens have been proposed by expert groups, however, there is no established consensus on

the number of serotypes or the specific serotypes that should be assessed. Diagnostic laboratories differ in their assay methods and in the number of selected pneumococcal serotypes (analyzed individually or in combination). A recent study has defined specific antibody deficiency (SAD) as an adequate IgG antibody response to less than 50% of 12 pneumococcal serotypes tested four weeks after vaccination with Pneumovax®, the 23-valent unconjugated pneumococcal vaccine, where an adequate IgG antibody response was defined as a post-immunization titre of ≥1.3mg/ml or four times that of the preimmunization value.[7] The vaccine literature uses a cut off of 0.35mcg/ml in healthy infants and >1.0mcg/ml in high risk populations as a protective titre against pneumococcal disease, however these data are derived from studies using Prevenar, and may not be relevant to the evaluation of functional Ig responses to polysaccharide antigens. Criteria for the interpretation of functional antibody responses to polysaccharide antigens will continue to be refined and informed by research findings.

If antibody responses to the unconjugated pneumococcal vaccine (Pneumovax) are reduced according to the criteria described above, one should proceed to immunize with a conjugated pneumococcal vaccine (Prevenar) to determine whether there is any antibody response to the protein-conjugated pneumococcal antigens. If present, this approach will also provide some protection against pneumococcal infections. It has been suggested that if the specific antibody response to protein conjugated pneumococcal antigens is deficient in addition to having poor polysaccharide antigen responses, this suggests a more severe antibody deficiency such as CVIDs.[8] Reimmunisation with a second dose of conjugated pneumococcal vaccine may also be considered if the response to the initial vaccine is unsatisfactory.

b) IgG subclasses

As with the evaluation of specific antibody responses, the interpretation of IgG subclasses is fraught with difficulties (see Chapter 4). Importantly, the finding of isolated low IgG subclass levels may not be clinically significant since individuals with complete absence of IgG subclasses due to gene deletions may remain entirely asymptomatic. However, if reduced IgG subclass levels are also accompanied by the presence of low or absent response to specific protein and/or polysaccharide antigens, and/or a low serum IgA level, this may bear more significance.

Stage 5

Other immune investigations

If XL or AR hyper-IgM syndrome is suspected, further analysis for CD40L (XL hyper-IgM) and CD40 (AR hyper-IgM) expression should be performed to confirm these diagnoses. Other diseases that lead to a similar phenotype of low IgG and IgA with normal or elevated IgM include Activation-Induced Cytidine Deaminase (AICDA) and Uracil-N-Glycosylase (UNG) defects (see figure 2b).[9]

Severely reduced CD19 expression with normal number of B cells enumerated using an antibody against CD20 indicates a diagnosis of CD19 deficiency.[10]

The heterogeneity of CVIDs has prompted classification schemes using detailed phenotyping of B-cell subpopulations, including switched memory B cells (IgD-IgM-CD27^{+}) and CD21^{low} B cells.[11] The consensus EUROclass classification scheme defines subgroups of patients with CVIDs. It is based on flow cytometric B cell phenotyping and separates patients into the following groups:

- Nearly absent B cells (<1%) - includes all patients with severe defects in B cell differentiation
- Severely reduced switched memory B cells (<2%) - indicates a defective germinal centre development as found in ICOS or CD40L deficiency and is associated with a higher risk for splenomegaly and granulomatous disease
- Expansion of transitional B cells (>9%) - associated with lymphadenopathy
- Expansion of CD21^{low} B cells(>10%) - associated with splenomegaly

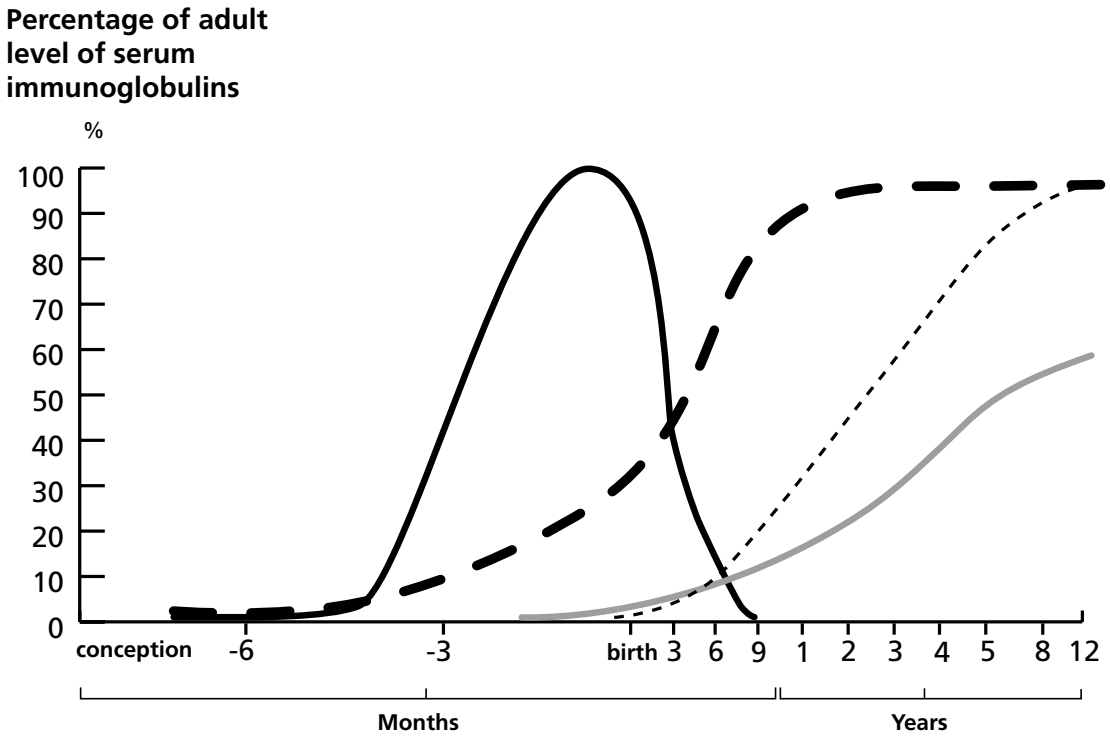
This concept for classification of CVIDs defects is still evolving. Such detailed flow cytometric analyses of B cell populations are largely performed in research settings and are not widely available in clinical practice.

Stage 6

Genetic studies

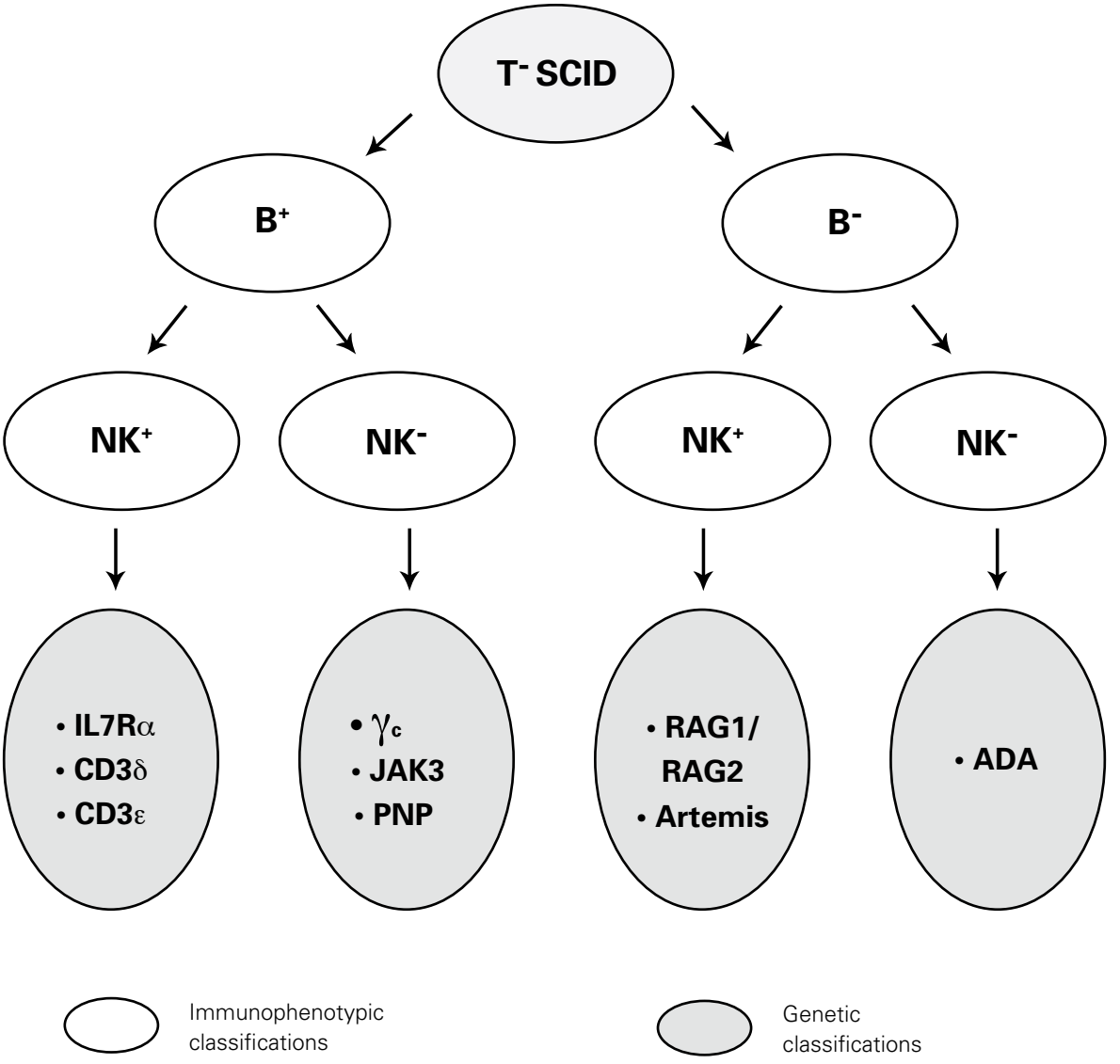
Genetic testing may help define and classify PIDs[12] and direct appropriate treatments including antenatal diagnosis and genetic counseling (Figure 2).

Figure 1
Kinetics of antibody production in childhood



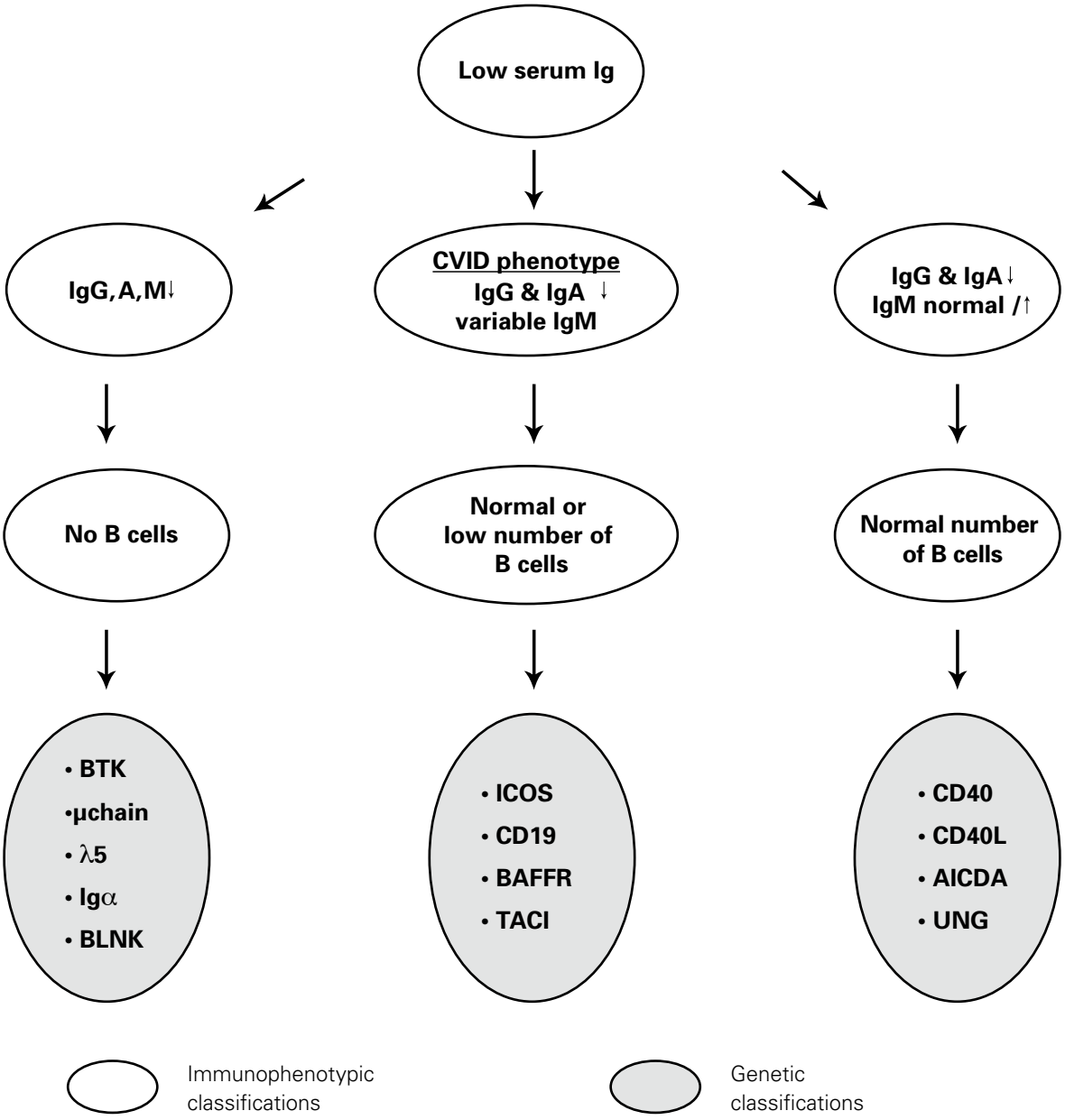
Modified from Stiehm ER, Fundenberg HH. Serum levels of immune globulins in health and disease. A survey. Pediatrics 37:715, 1966.

Figure 2a
Immunophenotypic and genetic classifications of severe combined immunodeficiency (SCID)



ADA adenosine deaminase;
JAK3 Janus kinase 3;
NK natural killer cells;
γc common gamma chain;
PNP purine nucleoside phosphorylase;
RAG recombinase activating gene

Figure 2b
Immunophenotypic and genetic classifications of predominantly antibody deficiencies



AICDA activation-induced cytidine deaminase;
BLNK B cell linker;
CVID common variable immunodeficiency;
Ig immunoglobulin;
UNG uracil-N-glycosylase

BAFFR B cell activating factor belonging to the TNF family receptor;
BTK Bruton tyrosine kinase;
ICOS inducible costimulator;
TACI transmembrane activator and calcium modulator and cyclophilin ligand interactor

References

1. Bonilla FA, Bernstein L, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP, Orange JS, Routes JM, Shearer WT, Sorensen RU. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94:S1-S63.

2. Wood P, Stanworth S, Burton J, Jones A, Peckham DG, Green T, Hyde C, Chapel H on behalf of the UK Primary Immunodeficiency Network. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. Clin Exp Immunol 2007;149(3):410-423.

3. Lau YL, Jones BM, Ng KW, Yeung CY. Percentile ranges for serum IgG subclass concentrations in healthy Chinese children. Clin Exp Immunol 1993;91(2):337-341.

4. Schaffer AA, Salzer U, Hammarstrom L, Grimbacher B. Deconstructing common variable immunodeficiency by genetic analysis. Curr Opin Genetics Devel 2007;17:201-212.

5. Folds JD, Schmitz JL. Clinical and laboratory assessment of immunity. J Allergy Clin Immunol 2003;111:S702-711.

6. Cunningham-Rundles C. Common variable immunodeficiency. Curr Allergy Asthma Report 2001;1:421-9.

7. Boyle RJ, Le C, Balloch A, Tang MLK. The clinical syndrome of specific antibody deficiency in children. Clin Exp Immunol 2006;146:486-492.

8. Goldacker S, Draeger R, Warnatz K, Huzly D, Salzer U, Thiel J, Eibel H, Schlesier M, Peter HH. Active vaccination in patients with common variable immunodeficiency (CVID). Clin Immunol 2007;124:294-303.

9. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120:776-794.

10. Van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJM, van Tol MJD, et al. An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med 2006;354;18:1901-1912.

11. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood 2008;111(1):77-85.

12. Piirila H, Valiaho J, Vihinen M. Immunodeficiency mutation databases (Idbases). Human Mutations 2006;27(12):1200-1208.

Chapter 3

Immunoglobulin replacement therapy for primary antibody deficiency with reduced serum immunoglobulin levels

- Serum levels of immunoglobulin isotypes may be reduced or normal (see chapter 4) in the primary antibody deficiencies
- The primary antibody deficiencies with severe reduction of serum IgG will usually require lifelong immunoglobulin replacement therapy
- CVIDs are a group of heterogeneous conditions associated with failure of antibody production and diagnosis is made after excluding other known primary and secondary immune deficiencies
- Immunoglobulin replacement therapy is not indicated for isolated IgA deficiency

Primary antibody deficiencies comprise a heterogeneous group of diseases (see chapter 1), in which failure to produce protective antibodies almost always results in recurrent bacterial infections. Lack of antibody production may be due to 1) failure of pre B cells to differentiate into mature antigen sensitive B cells, 2) defective B cells unable to respond to activation signals (for example common variable immunodeficiency disorders; CVIDs) or 3) inadequate T cells unable to provide the required signals to B cells that induce class switch from IgM to IgG and IgA production. There is heterogeneity within each of these three groups, due to differences in underlying immunopathogenesis and variable prognoses.

There are also primary antibody deficiencies associated with non-lymphoid abnormalities, in which a single gene mutation and/or several gene polymorphisms result in syndromes that include the presence of primary antibody deficiency; these are discussed later in Chapter 5.

B cell differentiation defects, including XLA

These are a group of single gene diseases that result in defects of B cell differentiation and a lack of mature B cells, which can be readily demonstrated by flow cytometry. Mutations have been identified in a number of genes coding for receptors involved in the recognition of differentiation signals, growth factors, essential cytokines, transcription factors, proteins required for immunoglobulin gene rearrangement, or signal transduction molecules. So far, in addition to those in the *BTK* gene, defects in the *BLNK*, μ heavy chain, lambda $_{5/14.1}$ of the surrogate light chain ($\lambda_{5/14.1}$) and IgA genes have also been identified, and more will likely follow as not all patients with absent circulating B cells are yet accounted for by these identified gene defects. Regardless of the underlying gene defect, these conditions are all managed in the same way, with replacement immunoglobulin therapy. The prototype condition, X-linked agammaglobulinaemia (XLA) is the only condition in this group that is X-linked, the others being inherited as autosomal recessive conditions, polygenic with susceptibility polymorphisms (in the case of CVIDs).

Description of the condition

These diseases typically present in children beyond the first 6 months of life once protective maternal antibody has been metabolised. Children present with recurrent and/or severe bacterial infections, with associated low serum IgM, IgA and IgG, failure of primary antibody production and absent B cells. In XLA, a family history is only identified in approximately 50% of cases, as there is an unusually high rate of new mutations affecting the *BTK* gene. It is thought that there is a higher incidence of earlier and more serious infections and bronchiectasis in the autosomal recessive (AR) diseases than in XLA.[1,2] Girls with the AR conditions have presented around a year of age, the majority with life-threatening infections, though this may broaden out (as in XLA) once more children have been described.

Diagnostic features

Low serum levels of IgM, IgA and IgG [usually IgG <1 g/l; IgA and IgM are <0.07 g/l].[3] Levels should be measured on at least two occasions to confirm the diagnosis.

A normal IgG in the neonatal period does not exclude the diagnosis of these conditions. Specific antibodies to immunisation antigens and common infectious organisms are typically absent, as are isohaemagglutinins. Some antigen specific antibodies may be detected at the onset of disease; however, these are lost progressively over time. It is not necessary to perform detailed evaluation of functional antibody responses with test immunisations if the diagnosis is secured by the absence of specific antibodies following infection and a lack of circulating B cells).[4] Lack of obvious lymphoid tissue (especially tonsils) is a helpful clinical feature; presence of tonsils usually excludes XLA. Lack of B cells, plasma cells, and germinal centres in lymphoid tissues (including bowel biopsies) is also seen on histological examination, however demonstration of these findings on biopsy is not required to make a diagnosis.

When to commence treatment

Once diagnosed, the patient requires Ig replacement therapy. Administration of Ig when there is active infection may be associated with a higher incidence of mild to moderate adverse reactions (5% reaction rate amongst subjects with infection vs 0.4% reaction rate amongst subjects without infection).[5] Some authorities recommend delaying the administration of Ig replacement until after infection is controlled with antibiotics for this reason (see chapter 7: Approach to immunoglobulin replacement).

Duration of therapy

In the absence of a "cure" (for example gene therapy or human stem cell transplantation for provision of normal B cell progenitors), replacement immunoglobulin therapy is life-long.

Common Variable Immunodeficiency Disorders (CVIDs)

Description of condition

These are a group of heterogeneous conditions associated with failure of antibody production, resulting in recurrent bacterial infections. The aetiology of these conditions is unknown, although they are thought to involve several genes (polygenic) with susceptibility polymorphisms. These conditions are characterised by reduced serum levels of IgG and IgA isotypes, with normal or low levels of circulating B cells and variable IgM levels. Typically, IgG levels are severely reduced. They present in adults of all ages as well as in children; some patients have a long history of infections whilst others may have gradual onset of symptoms, reflecting insidious onset of antibody failure. Though most patients present with respiratory or intestinal bacterial infections, some patients present with non-infective complications (such as autoimmune cytopenias or lymphoid infiltration) and patients presenting with granulomatous complications have been misdiagnosed as having sarcoidosis.

Whilst a very few are due to mutations in non-redundant genes (CD19) others are thought to be polygenic and therefore due to multiple polymorphisms of B cell genes (such as TACI, BAFFR or currently unknown genes) possibly in association with polymorphisms in T cell genes whose products are required for isotype switching.[6]

Diagnostic features

A diagnosis of CVIDs is made only after exclusion of other defined primary antibody deficiencies and all secondary causes of antibody deficiency. Other primary complex combined T & B cells syndromes, such as WAS and others in which antibody failure is a part, must also be excluded.

The following diagnostic criteria were proposed by expert groups with the intention to inform research studies,[3] however they form a useful basis for clinical diagnosis.

1. Patient is > 4 years of age
2. Serum IgG and IgA levels are below the normal ranges for age; IgM levels are normal or low, rarely undetectable. Levels should be measured on at least two occasions, 4 to 6 weeks apart.
3. There are usually detectable B cells [>1%] in the circulation. However, the recent Euroclass classification describes a subgroup of CVIDs with <1% B cells.[7] Levels should be measured on at least two occasions 4 to 6 weeks apart.
4. A failure of specific antibody production after natural antigen exposure (eg: childhood illnesses such as measles or chickenpox, hepatitis A, etc) and/or a lack of specific antibody production following immunisation is demonstrated. If antigen specific antibody levels are low initially, immunisation with licensed vaccines, followed by repeat measurement of specific antibody levels 4 weeks later, should be performed to confirm failure of antibody production. This may not be necessary for those patients with markedly reduced IgG levels. Appropriate isohaemagglutinins are low in titres or absent. Absence of antibodies to rubella, measured early in pregnancy, are often a useful clue.
5. Other causes of secondary antibody deficiencies, including lymphoid malignancy, drug-induced antibody deficiencies (anticonvulsants, anti-rheumatics and immune suppressants), renal or gut protein loss are excluded.

When to commence treatment

This is straightforward for those CVIDs patients who suffer recurrent infections (the majority). Once the diagnosis is confirmed, the patient requires immunoglobulin replacement therapy. It is usual, in the presence of chronic infection or bronchiectasis, to cover the patient with an appropriate antibiotic until immunoglobulin replacement therapy is established. For those patients who meet the diagnostic criteria but in whom recurrent or severe infections are not evident or the bacterial nature of recurring infections is not clear, evaluation of specific antibody responses to test immunisations is required to assist with the decision of when to commence treatment. In these patients, a period of observation may be considered and prophylaxis with antibiotics considered for a trial period but only if appropriate.

Less commonly, patients present with an autoimmune or lymphoproliferative complication of CVIDs in the absence of obvious recurrent infections. In this circumstance, the patient may benefit from a trial of immunoglobulin therapy for a period of one year (to include all seasons in case of seasonal variation in infections). Relief from symptoms previously ignored by the patient (such as chronic sinus infection or acute on chronic chest infections) can be revealing in terms of assessing whether there has been reduced morbidity following trial immunoglobulin therapy.

Duration of therapy

For patients in whom Ig replacement therapy has been commenced in the setting of recurrent infections, replacement immunoglobulin therapy is life-long.

Hyper-IgM syndromes

Description of condition

This is a group of single gene diseases with X-linked (CD40 ligand deficiency) or autosomal recessive inheritance. These diseases are due to abnormal T cells (CD40 ligand deficiency) or abnormal T-B cell interactions (CD40 deficiency) and may be classified as combined immune deficiencies. Failure of T cells to induce B cell class switching from IgM to IgG and IgA production results in an associated failure of IgG and IgA antibody production, and loss of somatic hypermutation to provide increased affinity for antigens. This results in excessive bacterial infections. Intrinsic defects in the downstream B cell signalling pathways that lead to immunoglobulin class switching and the generation of increased antibody diversity and affinity are also included in this group of diseases (for example AID, UNG and others likely to be identified).

These conditions usually present in children and rarely in adults. Most patients present with respiratory or intestinal infections. A common presentation in infancy is with Pneumocystis jiroveci (*carinii*) (PCP) pneumonia.

Less common presentations include lymphoid hyperplasia and unexplained abnormalities in liver function (for example sclerosing cholangitis).

Diagnostic features

Low serum levels of IgA and IgG (usually IgG <1 g/l, IgA <0.07 g/l) and normal or raised levels of IgM. [3] Levels should be measured on at least two occasions. IgG specific antibodies to natural exposure and immunisation antigens are absent, though IgM isohaemagglutinin levels are usually normal. Evaluation of specific antibody responses would not be required if IgG levels are markedly reduced.

Circulating B cell numbers are normal. For CD40 ligand deficiency, monoclonal antibodies are used to detect CD40L protein on activated T cells in vitro. Absence of CD40L protein is diagnostic, but if CD40L protein is detected, diagnosis can be made if there is failure of T cells to bind a CD40 construct on activation in vitro. Molecular confirmation is essential. Defects in the downstream B cell pathways are diagnosed by gene sequencing in expert centres.

Lack of, or giant, germinal centres in lymphoid tissues are indicative of CD40 ligand deficiency or AID/UNG deficiency, respectively, and deranged lymph node architecture such as follicular hyperplasia are a clue to these defects which also result in somatic hyper-mutation.[8,9]

When to commence treatment

Once the diagnosis is confirmed, the patient requires immunoglobulin replacement therapy.

Duration of therapy

In the absence of a "cure" (provision of normal progenitors for B cells by human stem cell transplantation(HSCT)), replacement immunoglobulin therapy is life-long. There is a considerable decrease in life expectancy for patients with CD40 ligand deficiency as a result of liver disease secondary to Cryptosporidia infections or malignancy.

HSCT has been reported to be successful in CD40 ligand deficiency and may be considered in boys with this disease.[10] If HSCT is successful in CD40 ligand deficiency, and normal immunoglobulin synthesis can be demonstrated, Ig replacement can be discontinued.

Selective IgA deficiency with recurrent infections

Selective IgA deficiency (in the absence of other evidence of impaired humoral immunity) with recurrent infection is not an indication for IRT.[11] Immunoglobulin replacement therapy products do not contain appreciable amounts of IgA.

References

1. Plebani A, Soresina A, Rondelli R, Amato G, Azzari C, Cardinale F, et al. Clinical, Immunological and molecular analysis in a large cohort of patients with X-linked agammaglobulinaemia: an Italian multicenter study. Clin Immunol 2002;104:221-230.
2. Conley M. Autosomal recessive agammaglobulinaemia. Primary Immunodeficiency Diseases - a molecular and genetic approach. Edited by Ochs H, Smith CIE, Puck JM 2007;2e:304-312.
3. Conley ME and Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999;93:190-7.
4. Chapel HM and Webster, ADB. Assessment of the immune system. Primary Immunodeficiency Diseases - a molecular and genetic approach. Edited by Ochs H, Smith CIE, Puck JM 2007;2e: 611-632.
5. Brennan VM, Salomé-Bentley NJ, Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol 2003;133(2):247-51.
6. Geha R, Notarangelo L, Casanova J, Chapel H, Conley M, Fischer A, Hammarström L, Nonoyama S, Ochs H, Puck J. Primary immunodeficiency diseases: An update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Clin Immunology 2007;120:776-794.
7. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood 2008;111(1):77-85.
8. Durandy A, Revy P, Fischer A. Autosomal hyper-IgM syndromes caused by an intrinsic B cell defect. Primary Immunodeficiency Diseases - a molecular and genetic approach. Edited by Ochs H, Smith CIE, Puck JM. 2007;2e:269-278.
9. Notarangelo LD, Peron S, Durandy A. Defects of class-switch recombination. J Allergy Clin Immunol 2006;117:855-64.
10. Gennery AR, Khawaja K, Veys P, Bredius RG, et al. Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993-2002. Blood 2004;103(3):1152-7.
11. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94:S1-63.

Chapter 4

Immunoglobulin replacement therapy for primary antibody deficiencies with normal serum immunoglobulin levels; and for transient hypogammaglobulinaemia of infancy

- Immunoglobulin replacement therapy (IRT) is seldom required when the serum IgG level is normal
- Specific antibody deficiency (SAD) describes an immunodeficiency characterised by failure of antibody response to antigenic challenge
- There is a lack of evidence to provide clear guidance on the efficacy of IRT in SAD
- In general, IRT is not indicated for isolated IgG subclass deficiency with normal specific antibody responses to vaccine antigens
- Transient Hypogammaglobulinaemia of Infancy (THI) is a diagnosis that can only be confirmed in retrospect after the reduced immunoglobulin levels return to normal
- Most children with THI do not require IRT

There are a number of conditions where antibody production is abnormal despite the presence of normal serum levels of IgG, IgA and IgM. These include specific antibody deficiency (SAD) and IgG subclass deficiency.

In these conditions the use of IRT is controversial and not routinely recommended as first line therapy, but may be considered in some situations. The use of IRT is also controversial in the condition Transient Hypogammaglobulinaemia of Infancy (THI), where levels of serum immunoglobulin are transiently reduced.

This chapter will discuss the above conditions where use of IRT is controversial. Conditions in which there is no indication for the use of replacement immunoglobulin therapy are also discussed.

Individuals with specific antibody deficiency (SAD) or low levels of IgG subclasses vary greatly in their susceptibility to infection and present a clinical challenge. In general, consensus case definitions are lacking. Furthermore, there may be important overlap between conditions – for example, a proportion of patients with IgG subclass deficiency and IgA deficiency have abnormal antibody production to specific antigens.[1-3]

These conditions are relatively common. In the Australasian Society for Clinical Immunology and Allergy Primary Immune Deficiency (PID) Register of Australia and New Zealand[4] IgG subclass deficiency and SAD accounted for 39.1% of antibody deficiency disorder registrations, with IgG subclass deficiency being the most common (25.1%).[4] IgG subclass deficiency and SAD accounted for 26.5% of total IRT within the Register.[4]

The importance of antibody deficiency disorders with normal serum IgG within the spectrum of antibody deficiency disorders is highlighted by the relative frequency of these conditions and the lack of evidence based guidance regarding the appropriateness of immunoglobulin replacement therapy. Further studies are required.

Specific Antibody Deficiency

Description of the condition

Specific antibody deficiency is a condition characterised by impaired production of antibodies

to specific antigens, usually polysaccharide, despite normal total IgG levels and normal B cell numbers.[5-7] Typically this condition is only considered when there is a clinical presentation with repeated or severe infections. Failure of antibody response to vaccine antigens (polysaccharide or protein) may be a feature of diverse primary immunodeficiencies, but the term specific antibody deficiency is usually reserved for those individuals in whom other PID disorders have been excluded. The term "specific" antibody deficiency has been used interchangeably with "functional" antibody deficiency, although it may also be used more precisely to describe defective antibody responses to T-independent unconjugated polysaccharide antigen challenge only.

Diagnostic features

Consensus case definitions have not been established. Published studies suggest that a diagnosis of SAD may be made if there is both recurrent and/or severe infection (typically sinopulmonary infections, purulent otorrhoea and bronchiectasis) AND an inadequate specific IgG response to >50% of polysaccharide antigens assessed.[8] An inadequate IgG response to a polysaccharide antigen may be defined as a post immunisation titre (four weeks after immunisation with Pneumovax®) of <1.3µg/ml or less than four fold higher than the pre-immunisation titre (see Chapter 2 and section on interpretation of test results below). Although these criteria for an adequate response are applied in both paediatric and adult patients, further studies are required to confirm the validity of this approach.

Controversy surrounding specific antibody deficiency

Patients with specific antibody deficiency can present a diagnostic challenge.[1,9] The use of vaccines as challenge systems to assess the competence of humoral immunity in humans has become widespread in clinical immunology. These assays are attractive because they measure a dynamic *in vivo* response of the immune system. However, measurement of vaccine responses are commonly used with the intention of identifying individual patients who might be suitable candidates for the use of IRT, to the exclusion of those with a normal response. It is important to critically examine the limitations of the evidence underlying this practice.

1. There is a general lack of prospective population based studies of vaccine non-responders. Pneumococcal vaccine non-responsiveness in otherwise healthy individuals may not necessarily represent a state of increased susceptibility to infectious morbidity or mortality.
2. Antibody responses to unconjugated pneumococcal vaccines vary widely among normal subjects[10] and vary with the characteristics of the vaccinee population[11] including age.[12]
3. Protective function may correlate with avidity better than antibody level.[11]
4. Although efforts to improve standardisation are underway, performance characteristics of individual laboratory methods, choice of serotypes and quality control programs remain variable.
5. Prior use of 7-valent pneumococcal polysaccharide-protein conjugate vaccine (Prevenar®) may invalidate the subsequent use of an unconjugated vaccine in the assessment of T-independent humoral immunity.[13]

Recommendations

1. Testing:

In patients over two years of age with a normal serum total IgG who experience frequent or persistent bacterial sinopulmonary infections or suppurative otitis media for at least six months, antibody responses to specific antigens (eg vaccines) should be evaluated. Blood samples should be collected at baseline and at four weeks post vaccination. Unconjugated pneumococcal vaccine (Pneumovax®) challenge is recommended as anticapsular polysaccharide responses can be assessed and *Pneumococcus* is a common respiratory tract pathogen in PID. Testing of vaccine responses should be performed in a specialised laboratory and responses examined to as many serotypes as possible using standardised reagents and assay methodologies. Many reference laboratories offer 12 pneumococcal serotypes. Antibody responses to protein antigens (tetanus and diphtheria) are rarely abnormal in the setting of normal responses to polysaccharide (see Chapter 2).

2. Interpretation of antibody response results:

Interpretation of the antibody response can be difficult. It is recommended that a diagnosis of

specific antibody deficiency can be suspected if following 23-valent unconjugated pneumococcal immunisation there is an adequate response to <50% of 12 pneumococcal serotypes tested. An adequate response is defined as a post-immunisation antibody concentration of 1.3µg/ml or greater, or a four-fold increase over the preimmunization value for that serotype.[8,12]

When to commence treatment

There is a lack of evidence to provide clear guidance on the efficacy of IRT in SAD. Many patients with specific antibody deficiency will not require Ig replacement for control of bacterial infections.[1] If there are severe or recurrent bacterial infections involving the sinopulmonary tracts, initial management with prophylactic antibiotics should be commenced. Immunoglobulin replacement therapy may be considered where patients continue to experience recurrent infection despite prophylactic antibiotic therapy.[9,14] Commonly used oral antibiotics include cotrimoxazole, and macrolides.

Patients may benefit from immunisation with a conjugated pneumococcal vaccine[1], which may provide an additional opportunity for assessment of functional immunity (see chapter 2) and also provide some protection against pneumococcal infection. In rare cases of severe end-organ damage such as bronchiectasis in the presence of unequivocal failure of vaccine responses, IRT should be commenced immediately without a prior trial of antibiotic therapy.

Duration of therapy

The natural history of SAD is not known. It is recommended that patients receive one to two years of therapy followed by cessation and repeat immunological evaluation once replacement immunoglobulin has been cleared (at least six months from last infusion). Patients should be monitored for clinical response to IRT relying principally on frequency and severity of infections, antibiotic dependence and the development of end-organ damage. However, further infectious episodes may not necessarily indicate IRT failure, as pre-existing airway damage may predispose to continuing infections. A trial of cessation of therapy will also allow evaluation of treatment effect. In temperate climates it is common to cease therapy in the spring-summer months due to the reduced likelihood of infection during these months. Re-evaluation of immune response with vaccine challenge should be performed six months after cessation of immunoglobulin replacement when treatment immunoglobulin has been cleared. During this period it is important to document infection rates and the need for antibiotics. Patients experiencing severe organ or life-threatening infections during these months may have immunoglobulin replacement therapy recommenced immediately (see chapter 8).

IgG subclass deficiency

Description of the condition

The clinical significance of abnormal IgG subclass levels in patients with increased susceptibility to infection is unclear. In these individuals, additional immune defects such as IgA deficiency and impaired responses to vaccine antigen challenge may be present.[1,15] IgG subclass deficiency may be first detected in individuals who subsequently evolve to CVIDs.[1]

Diagnostic criteria

In the absence of evidence supporting isolated IgG subclass deficiency as a disease state with significant morbidity, diagnostic criteria are not justified. Individuals with recurrent infection and abnormally low levels of one or more IgG subclasses should be further evaluated by assessing functional antibody responses (see Specific Antibody Deficiency).

Controversy surrounding IgG subclass deficiency

IgG subclass deficiency is a recognised immunodeficiency [6] but its clinical significance as an isolated finding is in doubt. Arguments against the idea that abnormalities of IgG subclasses define a distinct disease include:[16]

1. Isolated finding of low levels of one or more IgG subclasses does not identify individuals at risk of developing severe recurrent bacterial infections.[15]

2. Lack of reproducibility of IgG subclass assays and lack of well standardised age-specific reference ranges.

3. Data on the natural history of IgG subclass reductions in children are not available.

4. Individuals with γ–heavy chain deletions of one or more IgG subclasses are generally asymptomatic.

5. Normal polysaccharide antibody responses may be detected in IgG_2 subclass deficient individuals.

Recently a large, uncontrolled, retrospective study of IRT in 350 adult patients with IgG subclass deficiency reported that in patients with 4 or more antibiotic-demanding respiratory tract infections per year at baseline, 69.7% experienced a greater than 50% reduction in the rate of such infections on IRT.[17] Response was similar between patients with chronic lung disease and those without. However this study was retrospective and did not include a control group. Therefore, it is not possible to conclude that the clinical benefit was attributable to IRT. Also, vaccine responses were not systematically evaluated so it is not known whether broader defects of antibody function were present in these patients.

When to commence treatment

There is a lack of evidence to provide clear guidance on the efficacy of IRT in IgG subclass deficiency. In general, the finding of isolated IgG subclass deficiency is seldom sufficient grounds for commencement of immunoglobulin therapy. A trial of IRT may be considered if functional antibody responses are deficient AND there is bronchiectasis or significant infection recurring despite prophylactic antibiotic therapy (see Specific Antibody Deficiency).

Transient Hypogammaglobulinaemia of Infancy

Description of the condition

Transient hypogammaglobulinaemia of infancy (THI) has been defined as persistently low immunoglobulin levels in an infant older than six months in whom other immunodeficiencies have been excluded.

Diagnostic criteria

The usual findings are reduced IgG levels (70% subjects) with or without reduced IgA levels (95% subjects).[18] The incidence is uncertain, however this condition appears to be common relative to other primary immunodeficiency syndromes. A predominant phenotype seen is male infants with otitis media and wheezing. THI is also associated with atopy.[19]

The majority of infants with THI have normal or near normal responses to protein antigens such as tetanus and diphtheria which distinguishes the condition from other more profound immunodeficiencies.[20] Recovery of the immunoglobulin levels to normal generally occurs by 18 months of age. More recently a cohort of children was described in which the normalisation of immunoglobulins commonly occurred after the period of infancy.[18] Of those whose immunoglobulins normalised, only 48% occurred in infancy and normalisation was significantly delayed in females as compared to males. It was suggested that a more appropriate term for such cases may be "hypoimmunoglobulinaemia of early childhood". This is a diagnosis that can only be confirmed in retrospect after the reduced immunoglobulin levels return to normal.

When to commence treatment

Most children with THI do not require IVIg treatment. If a more severe life-threatening infection such as meningitis or pneumonia has occurred or there is ongoing bacterial respiratory infection despite prophylactic antibiotic therapy, a trial of IVIg for 6-12 months is indicated.

Clinical settings for which IRT is not recommended

Use of IRT for primary prevention of infections

Patients who do not experience recurrent, severe or unusual infections in whom laboratory abnormalities have been detected incidentally do not meet appropriate criteria for IRT. Common examples of laboratory abnormalities include Selective IgA deficiency, and low levels of IgG subclasses. IRT in these circumstances would represent a primary prevention strategy, and there is insufficient data on future infectious risk in the natural history of subjects with these findings to support IRT use.

Secondary prevention of infections in the absence of laboratory evidence of impaired humoral immunity

Recurrent infection with normal humoral immune function by currently available tests eg idiopathic bronchiectasis, is not an indication for IRT in the absence of clinical trials demonstrating benefit.

References

1. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94(5 Suppl 1):S1-63.

2. Cheng YK, Decker PA, O'Byrne MM, Weiler CR. Clinical and laboratory characteristics of 75 patients with specific polysaccharide antibody deficiency syndrome. Ann Allergy Asthma Immunol 2006;97(3):306-11.

3. Edwards E, Razvi S, Cunningham-Rundles C. IgA deficiency: clinical correlates and responses to pneumococcal vaccine. Clin Immunol 2004;111(1):93-7.

4. Kirkpatrick P, Riminton S. Primary Immunodeficiency Diseases in Australia and New Zealand. J Clin Immunol 2007;27:517-24.

5. Ambrosino DM, Siber GR, Chilmonczyk BA, Jernberg JB, Finberg RW. An immunodeficiency characterized by impaired antibody responses to polysaccharides. N Engl J Med 1987;316(13):790-3.

6. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120(4):776-94.

7. Saxon A, Kobayashi RH, Stevens RH, Singer AD, Stiehm ER, Siegel SC. In vitro analysis of humoral immunity in antibody deficiency with normal immunoglobulins. Clin Immunol Immunopathol 1980;17(2):235-44.

8. Boyle RJ, Le C, Balloch A, Tang ML. The clinical syndrome of specific antibody deficiency in children. Clin Exp Immunol 2006;146(3):486-92.

9. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4 Suppl):S525-53.

10. Go ES, Ballas ZK. Anti-pneumococcal antibody response in normal subjects: a meta-analysis. J Allergy Clin Immunol 1996;98(1):205-15.

11. Wernette CM, Frasch CE, Madore D, Carlone G, Goldblatt D, Plikaytis B, et al. Enzyme-linked immunosorbent assay for quantitation of human antibodies to pneumococcal polysaccharides. Clin Diag Lab Immunol 2003;10(4):514-9.

12. Sorensen RU, Leiva LE, Javier FC, Sacerdote DM, Bradford N, Butler B, et al. Influence of age on the response to Streptococcus pneumoniae vaccine in patients with recurrent infections and normal immunoglobulin concentrations. J Allergy Clin Immunol 1998;102(2):215-21.

13. Balmer P, Cant AJ, Borrow R. Anti-pneumococcal antibody titre measurement: what useful information does it yield? J Clin Path 2007;60(4):345-50.

14. Jurisdictional Blood Committee. Criteria for the clinical use of intravenous immunoglobulins in Australia. Canberra, Commonwealth of Australia 2007.

15. Maguire GA, Kumararatne DS, Joyce HJ. Are there any clinical indications for measuring IgG subclasses? Ann Clin Biochem 2002;39:374-7.

16. Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? Curr Allergy Asthma Report 2002;2:356-60.

17. Olinder-Nielsen AM, Granert C, Forsberg P, Friman V, Vietorisz A, Bjorkander J. Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. Scand J Infect Dis 2007;39(1):44-50.

18. Whelan MA, Hwan WH, Beausoleil J, Hauck WW, McGeady SJ. Infants presenting with recurrent infections and low immunoglobulins: characteristics and analysis of normalization. J Clin Immunol 2006;26(1):7-11.

19. Walker AM, Kemp AS, Hill DJ, Shelton MJ. Features of transient hypogammaglobulinaemia in infants screened for immunological abnormalities. Arch Dis Child 1994;70:183-6.

20. Tiller TL, Buckley RH. Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunologic features of 11 new cases and long-term follow-up. J Pediatr 1978;92:347-53.

Chapter 5

Immunoglobulin replacement therapy for primary immune deficiency with combined cellular and antibody deficiency

- Patients with combined immune deficiency have defects of T cell function as well as antibody deficiency
- Immunoglobulin replacement therapy (IRT) may be indicated for the antibody deficiency component
- In SCID, IRT should be initiated immediately the diagnosis is established
- IRT may be commenced in children with genetically confirmed XLP in the absence of hypogammaglobulinaemia or specific antibody deficiency
- IRT is indicated in classic Wiskott-Aldrich syndrome and has been shown to prolong life expectancy
- In Hyper IgE syndrome, Ataxia Telangectasia and DiGeorge syndrome, a trial of IRT should be considered in patients with recurrent sinopulmonary infection or severe lung disease and evidence of impaired specific antibody responses

There are a number of conditions with combined defects of T cell and B cell immune function[1]. Those with severe impairment of T cell function include severe combined immune deficiency (SCID), Omenn syndrome, and MHC class II deficiency. Some patients with T cell deficiencies have normal immunoglobulin levels but nevertheless have defects of antibody production (eg. purine nucleoside phosphorylase (PNP) deficiency, CD8 deficiency, MHC class II deficiency). Other combined immune deficiencies have a less profound impairment of T and B cell function, and include Wiskott-Aldrich Syndrome (WAS), Ataxia Telangiectasia (AT), and X-linked lymphoproliferative syndrome (XLP). This terminology can be confusing. Indeed, X-linked hyper-IgM syndrome and some forms of CVIDs involve combined defects of T and B cell function, but have been discussed in chapter 3.

Severe combined immunodeficiency (SCID)

Description of the Condition

SCID is a heterogeneous group of disorders associated with a profound defect of T and B cell function. As a result there is absence of specific immunity and severe susceptibility to a large range of common and opportunistic infections (bacterial, viral, fungal and protozoal). Without specific treatment, most patients die within the first years of life. Bone marrow transplantation is the definitive therapy once diagnosis is made, although gene therapy has been successful in some cases of X-linked and adenosine deaminase deficiency associated SCID. Prevention of infection with intravenous immunoglobulin and prophylactic cotrimoxazole (to prevent pneumocystis infection), aggressive treatment of infections, and use of irradiated, CMV negative blood products will all prolong short-term survival whilst awaiting definitive treatment.

Approximately 50-60% of cases are X-linked and due to mutations in the common γc chain. Most of the remainder are autosomal recessive, however the molecular defect in many cases has not yet been identified. Identified mutations are regularly updated.[2,3]

Most infants present in the first two to six months of life with opportunistic infection, especially pneumocystitis pneumonia. There is often chronic diarrhoea with resultant failure to thrive and persistent candidiasis. Severe eczematous rash may occur in association with graft-versus-host disease from maternally derived T cells or in Omenn syndrome.
There is an increased frequency of bacterial infections as transplacentally derived IgG wanes in the absence of production by the affected infant.

Diagnostic features

There is absence of tonsillar and lymphoid tissue and absence of a thymic shadow on chest X-ray. Most infants will have absent or profound reduction of IgA and IgM. IgG levels may not be reduced in the first few months of life, but are usually profoundly low thereafter. Lymphopenia is present in most cases, with T, B and NK cell numbers variably affected dependent on the molecular aetiology.[4] Of note, in some conditions such as Omenn syndrome, Bare Lymphocyte Syndrome or PNP deficiency, there are normal or elevated levels of total IgG, A and/or M but absence of specific functional antibodies. There is markedly reduced mitogen induced T-cell proliferative response.

When to commence treatment

Immunoglobulin replacement therapy should be initiated as soon as possible after the diagnosis is established, once hypogammaglobulinaemia is confirmed. A proportion of children will have incomplete immune reconstitution following bone marrow transplantation as a result of failure of B cell engraftment. These children will require ongoing replacement IVIg in the same way as other patients with primary humoral immunodeficiency (refer to Chapter 3).

Other well defined primary immunodeficiency syndromes where IVIg may be indicated

There are a number of combined immunodeficiencies in which the immune defect is not as profound as that found in most cases of SCID. The identification of the molecular basis of these disorders is expanding. Immunoglobulin replacement therapy is not necessarily indicated in these patients with combined immunodeficiency syndromes.

Wiskott-Aldrich Syndrome (WAS)

This X-linked disorder is characterised by thrombocytopenia (with small platelet size), eczema and recurrent infections. The syndrome is also associated with a substantial risk of auto-immune disorders and lymphoid malignancy. There is a progressive loss of T cell numbers and B cell function. The WASP protein (WASp) has roles in organisation of the cytoskeleton via regulation of actin polymerization, intracellular signalling, IgG-mediated phagocytosis and regulation of apoptosis. Presentation is variable ranging from classic WAS to isolated thrombocytopenia without immune deficiency (X-linked thrombocytopenia; XLT) and congenital X-linked neutropenia.[5]

Children with WAS often initially present with petechiae, bruising, and blood streaked stools associated with eczema which can be of variable severity. Recurrent ear infections often with purulent drainage commence by six months of age, followed by other sinopulmonary infections. Eczema is often complicated by secondary bacterial and viral skin infections. Patients are at increased risk of severe herpes, varicella and pneumocystis infections. A range of auto-immune diseases can occur, most commonly Coombs positive haemolytic anaemia and platelet autoantibodies which can exacerbate the thrombocytopenia. Severe thrombocytopenia may predispose to life-threatening haemorrhage. Thrombocytopenia and or neutropenia may occur in the absence of immune deficiency in XLT.

The characteristic laboratory finding in WAS syndrome is thrombocytopenia with small platelet size. B cell numbers are normal or proportionally elevated, even when lymphopenia develops (by 6-8 years). Immunoglobulin G, A and E levels are usually elevated whilst IgM is mildly to moderately reduced. There are poor specific antibody responses to polysaccharide antigens and usually also poor responses to protein antigens. Isohaemagglutinin levels are low. Natural killer cell function is impaired, contributing to the risk of severe herpes and varicella infection. The diagnosis can be confirmed by genetic testing or by detection of WASP proteins by Western Blot.

Replacement intravenous immunoglobulin (IVIg) therapy has been shown to substantially prolong life expectancy in WAS and is recognised standard therapy to prevent recurrent infection.[4] Splenectomy, when performed to prevent life-threatening haemorrhage, increases the risk of subsequent infection. Life-long

prophylactic antibiotic therapy must then be continued. High dose IVIg (2g/kg) and systemic steroids are sometimes used to treat auto-immune complications. Their effect on platelet counts however is minimal in the absence of splenectomy. Bone marrow transplantation is the only curative treatment, the best results occurring when performed at a younger age. There is no evidence that patients with the XLT phenotype benefit from antimicrobial prophylaxis or IVIg (Italian Primary Immunodeficiencies Strategic Scientific Committee recommendations for diagnosis and treatment of WAS/XLT 2004).[6]

Hyper-IgE Syndrome

The genetic defects associated with both autosomal dominant [7,8] and recessive forms [9,10] of Hyper-IgE syndrome have been recently described. Most cases are autosomal dominant (AD) or sporadic and have been found to be secondary to mutations in STAT3, a downstream mediator of IL6 signaling.[8] A rarer autosomal recessive form of hyper-IgE syndrome is associated with mutations in Tyrosine Kinase 2 (TYK2).[10] The AD or sporadic form of Hyper-IgE syndrome is characterised by chronic dermatitis, recurrent infections, skeletal abnormalities (osteopenia and delayed shedding of primary teeth), development of coarse facies and substantially elevated serum IgE levels. The dermatitis usually begins in early infancy and is pruritic but its distribution is atypical of atopic dermatitis, the commonest cause of a significantly elevated IgE at this age. Despite the high IgE levels and higher incidence of positive skin prick tests, food allergy, asthma and hayfever are uncommon. Staphylococcal infections are common. The skin infections in hyper-IgE syndrome tend to be deep eg furunculosis, and are often associated with minimal systemic toxicity. There is an increased frequency of sinopulmonary infection particularly pneumonia. Pneumatocoeles form secondary to recurrent staphylococcal pneumonia. Infections with *Candida albicans, Haemophilus influenzae, Streptococcus pneumoniae* and group A streptococci are also a common cause of recurrent sinopulmonary infections.

In most cases, serum antibody levels are elevated. However many individuals have impaired specific antibody responses to polysaccharide antigens which may be associated with poor responses to protein antigens as well.[11,12]

The mainstay of treatment is life-long, continuous anti-staphylococcal antibiotic and/or antifungal treatment to prevent infection. Surgical excision of pneumatocoeles may be required. There have only been case reports or single cases in small case series reports of patients with severe eczema demonstrating that some patients benefit from high dose (1-2g/kg) IVIg therapy,[13-15] and its role in this entity remains controversial. However, in patients with recurrent sinopulmonary infection or severe lung disease AND evidence of impaired specific antibody responses, a trial of IVIg 0.4g/kg monthly is warranted (see Chapter 4).

Ataxia telangectasia

This is an autosomal recessive condition secondary to mutations of the ATM gene on chromosome 11. The ATM protein has roles in signal transduction, intracellular protein transport and cell cycle control. Characteristic features include progressive neurodegeneration (ataxia and dysarthria), occular and cutaneous telangiectasia, immunodeficiency, premature aging and significant risk of malignancy. This is one of a group of related disorders termed the chromosomal breakage syndromes, which include Nijgemen breakage syndrome and DNA ligase I and IV deficiency.

Laboratory tests that can support the diagnosis are raised serum alpha-fetoprotein (AFP) and chromosomal fragility. Genetic testing is also available to confirm the diagnosis.

There is a variable degree of immune dysfunction. The most common immune defects in a cohort of 100 affected individuals were lymphopenia (71%), impaired mitogen induced T cell proliferation (35%), IgA deficiency (63%) often in association with low IgG_2 and impaired specific antibody responses (31%). In contrast, almost 10% develop hypergammaglobulinaemia, many with monoclonal bands on immunofixation. In contrast to the neurological progression, longitudinal data in this cohort demonstrated a lack of deterioration in immune status over time.[16] Recurrent mucopurulent upper respiratory tract infection occurs in a third of patients and recurrent otitis media in half of the patients. The incidence of lower respiratory tract infection increases with age, probably in association with neurological rather than immune deterioration. The incidence and severity of clinical infection with bacterial, viral and opportunistic infections is

significantly less than predicted by the measurable immune deficits.

Immunoglobulin replacement therapy in patients with significant infection reduces the severity and frequency of infections. Immunoglobulin replacement therapy is warranted in patients with recurrent infection AND evidence of a humoral immune defect.

DiGeorge Syndrome

DiGeorge syndrome results from a developmental defect in the third branchial pouch and fourth pharyngeal arch, classically causing typical facies, cardiac outflow tract defects, thymic and parathyroid hypoplasia, behavioural problems and developmental delay. Deletions of chromosome 22q11.2 are found in approximately 85% of patients and of chromosome 10p13-14 in a smaller number. There is great variability in the severity of clinical and immunologic defects.

Most patients have an increased susceptibility to otitis media and sinusitis, usually more a function of anatomic and functional airways compromise than of systemic immunodeficiency. The most common finding is a mild reduction in total T cell numbers (CD3), particularly of the CD4 subset, usually of no clinical significance. Complete absence of T cells resulting in a severe immune deficiency (complete DiGeorge) is rare.

Isolated IgA deficiency and specific antibody deficiency are not uncommon. However, panhypogammaglobulinaemia is rare. Children with DiGeorge syndrome have been reported to have a statistically significant reduction in circulating CD27+ B cells, particularly IgM+CD27+ cells with only mild reduction in switched memory B cells compared with age matched controls. IgM+(IgD+)CD27+ B cells produce high-affinity IgM antibodies in a T cell-independent manner and are involved in rapid response to polysaccharide antigens and the memory B cell defect may contribute to infection risk.[17]

Most children with recurrent otitis media and sinusitis only require early antibiotic therapy with or without prophylactic antibiotics. However, in those with recurrent or severe infection despite antibiotic prophylaxis AND evidence of impaired specific antibody responses, a trial of immunoglobulin replacement therapy 0.4g/kg monthly is warranted.

X-linked Lymphoproliferative syndrome (XLP)

This syndrome is characterised by vulnerability to adverse outcomes following EBV infection that manifests in 3 classic forms with significant overlap: fulminant infectious mononucleosis (50%), hypogammaglobulinaemia (30%) and lymphoma (25%).

A third of those with hypogammaglobulinaemia have hypogammaglobulinaemia before EBV infection and up to 10% of male patients diagnosed as having CVIDs may have mutations in SH2D1A (located at Xq25), the molecular basis of 60-80% of XLP. This gene encodes the adaptor protein SAP (signalling lymphocyte activation molecule (SLAM) – associated protein), the absence of which leaves a series of T and B cell proliferation signals unchecked. A second defect, a mutation in BIRC4 which encodes the X-linked inhibitor of apoptosis protein (XIAP) has recently been described.[18] Following infection with EBV, patients mount a vigorous, uncontrolled polyclonal expansion of T and B cells. Uncontrolled lymphocyte proliferation, organ infiltration, and T cell cytotoxic activity can lead to multiorgan failure, hepatic necrosis, bone marrow failure and death. An associated defect of NK cell cytotoxicity predisposes to haemophagocytosis and mutations in SH2D1A have been found in some cases of familial hemophagocytic lymphohistiocytosis. Survivors can develop hypogammaglobulinaemia with impaired specific antibody production, inverted CD4/CD8 ratio, and diminished in vitro T cell proliferative responses to mitogens and antigens.

Immunoglobulin replacement therapy (0.4g/kg monthly) is indicated in patients with XLP and hypogammaglobulinaemia and/or specific antibody deficiency to prevent recurrent infection and its sequelae. Although controversial, many clinicians would commence immunoglobulin replacement therapy in children with genetically confirmed XLP without hypogammaglobulinaemia or specific antibody deficiency. Although it may reduce the risk, it may not prevent primary EBV infection and relapses of EBV disease occur in patients while receiving immunoglobulin replacement therapy.[4,19] Bone marrow transplantation should be considered in patients who have experienced at least 1 life-threatening manifestation of XLP but is controversial before clinical disease has manifest.

Thymoma with Immunodeficiency (Good syndrome)

Good syndrome is a rare cause of combined B and T cell immunodeficiency that occurs in association with a thymoma. This sporadic disorder is most commonly seen in older adults of either sex (>40 years) and should be considered in the differential diagnosis of CVIDs. The classic scenario is radiological detection of the thymoma and subsequent recognition of hypogammaglobulinaemia, depleted B cells, diminished T cells and inversion of the CD4/CD8 ratio. In vitro T cell responses are impaired. The onset of immunodeficiency may precede the thymoma. Affected patients have increased susceptibility to bacterial, fungal, viral, and opportunistic infections. The most common infections are from candidiasis and herpes virus as well as common respiratory tract infections. Associated autoimmune disease is common (myasthenia gravis, pernicious anaemia, diabetes, thrombocytopenia). Immunoglobulin administration decreases the number of infections. Surgical removal of the thymoma may improve the autoimmune problems, but does not cure the immunodeficiency. Death usually occurs within a few years of diagnosis if the thymoma is malignant.[20]

References

1. Stiehm ER, O.H., Winkelstein JA. (Editors). Immunologic Disorders in Infants and Children 5th Edition 2004;15-18:447-604, ed.

2. Kalman L, Lindegren ML, Kobrynski, L, Vogt R, Hannon H, Howard JT, Buckley R. Mutations in genes required for T-cell development: IL7R, CD45, IL2RG, JAK3, RAG1, RAG2, ARTEMIS, and ADA and severe combined immunodeficiency: HuGE review. Genet Med, 2004;6:16-26.

3. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, Roifman C, Seger R, Geha RS for the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee, Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, *2005.* J Allergy Clin Immunol 2006;(117):883-96.

4. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson Jr RP, Orange JS, Routes JM, Shearer WT, Sorensen RU. Practice parameter for diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94:S1-63.

5. Notarangelo LD, Miao CH, Ochs HD. 2008; 15(1):30–36, Wiskott-Aldrich syndrome. Curr Opin Hematol 2008;15:30-36.

6. Italian Primary Immunodeficiencies Strategic Scientific Committee recommendations for diagnosis and treatment of Wiskott Aldrich Syndrome and X-linked thrombocytopenia (last updated 2004).

7. Minegishi Y, Karasuyama H, Hyperimmunoglobulin E syndrome and tyrosine kinase 2 deficiency. Curr Opin Allergy Clin Immunol 2007;7506-9.

8. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 Mutations in the Hyper-IgE Syndrome. N Engl J Med 2007;357:1608-19.

9. Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr 2004;144:93-9.

10. Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, et al. Human Tyrosine Kinase 2 Deficiency Reveals Its Requisite Roles in Multiple Cytokine Signals Involved in Innate and Acquired Immunity. Immunity 2006;25:745-55.

11. Leung DY, Ambrosino DM, Arbeit RD, Newton JL, Geha RS. Impaired antibody responses in the hyperimmunoglobulinemia E syndrome. J Allergy Clin Immunol 1988;81:1082-97.

12. Sheerin KA, Buckley RH. Antibody responses to protein, polysaccharide, and phiX174 antigens in the hypergammaglobulinemia E (hyper-IgE) syndrome. J Allergy Clin Immunol 1991;87:803-11.

13. Kimata H, High-dose intravenous gamma-globulin treatment for hyperimmunoglobulinemia E syndrome. J Allergy Clin Immunol 1995;95:771-4.

14. Wakim M, A.M., Yajima A, Speights D, Saxon A, Stiehm ER. High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. Ann Allergy Asthma Immunol 1998;81:153-8.

15. Bilora F, Petrobelli F, Boccioletti V, Pomerri F. Moderate-dose intravenous immunoglobulin treatment of Job's syndrome. Case report. Minerva Med 2000;91:113-6.

16. Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM. Immunodeficiency and Infections in Ataxia-Telangiectasia. J Pediatr 2004;144:505-11.

17. Finocchi A, Di Cesare S, Romiti ML, Capponi C, Rossi P, Carsetti R, Cancrini C. Humoral immune responses and CD27+ B cells in children with DiGeorge syndrome (22q11.2 deletion syndrome). Pediatr Allergy Immunol 2006;17:382-8.

18. Marodi L, Notarangelo LD. Immunological and genetic bases of new primary immunodeficiencies. Immunol, 2007;7:851-61.

19. Nelson DL, Terhorst C. X-linked lymphoproliferative syndrome. Clin Exp Immunol 2000;122:291-295.

20. Miyakis S, Pefanis A, Passam FH, Christodulakis GR, Roussou PA, Mountokalakis TD. Thymoma with immunodeficiency (Good's syndrome): review of the literature apropos three cases. Scand J Infect Dis 2006;38:314-9.

Chapter 6

Secondary causes of antibody deficiency

- The first priority is to treat the underlying disorder causing the antibody deficiency where possible
- Opinions vary on the use of IRT for these secondary causes of antibody deficiency
- IRT may be considered in patients with severe recurrent infection and profound hypogammaglobulinemia
- In HIV infection in children, antiretroviral therapy should be used as the first line treatment prior to considering IRT
- IRT is usually not helpful in protein losing states such as nephrotic syndrome and protein losing enteropathy
- Evaluation of specific antibody responses to vaccine antigens may assist in the decision to commence IRT

There are a number of conditions that may be associated with secondary antibody deficiency (Table 1). Immunoglobulin replacement therapy may be appropriate in certain situations but the evidence to support this is limited. The first approach to management of the antibody deficiency is to correct the underlying cause where possible. Indications for commencing IRT are discussed.

Haematological malignancies and lymphoproliferative disorders

Haematological malignancies and lymphoproliferative disorders may be associated with secondary immune deficiency either as a direct effect of the disease itself or due to drug therapy. Hypogammaglobulinaemia and impaired vaccine responses have been documented in chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM).[1,6] The exact mechanism(s) are not known but clonal proliferation of dysfunctional malignant B cells and plasma cells that suppress the normal cellular counterparts are likely. In addition, T cell responses may be impaired resulting in diseases such as herpes zoster, and neutropenia can be a complication of chemotherapy. The result is that infections are more common in these patients, but it is often difficult to tease out the effects of the disease itself versus those of drug therapy.

In the absence of chemotherapy, the majority of infections are bacterial with a predominance of encapsulated bacteria, for example pneumococcus, particularly in the early phases of the disease. Chemotherapy is associated with a broader spectrum of infections, including opportunistic infections, particularly if there is associated neutropenia. The pattern of infection in early CLL or plateau-phase MM mimics that seen in primary antibody deficiency.

Given the evidence for efficacy of immunoglobulin replacement in primary antibody deficiency there has been some interest in using immunoglobulin replacement in the haematological malignancies, particularly CLL and MM where hypogammaglobulinaemia is well documented. However because of the complexity of the underlying condition it cannot be assumed that replacement will be as efficacious as in primary hypogammaglobulinaemia.

Table 1
Conditions that may be associated with a secondary antibody deficiency
(either due to the condition or the treatment)

Haematological / Lymphoproliferative conditions	• Chronic lymphocytic leukaemia • Multiple myeloma • Lymphoma • Acute leukaemia
Infections	• Human immunodeficiency virus (HIV) • Congenital Rubella
Drugs	(See Table 2)
Transplantation	• Solid organ • Haemopoietic stem cell
Protein losing states	• Nephrotic syndrome • Protein losing enteropathy • Lymphangiectasia • Chylothorax • Severe burns
Prematurity	—

Studies to assess immunological function and likelihood of infection in subgroups of patients with haematological malignancies are generally lacking. There is no consensus on the best approach to assess infection risk and immunological status, although evaluation of specific response to immunisations has been suggested. The stage of disease may also be important when considering replacement immunoglobulin therapy. Advanced disease, as demonstrated in MM (see below), may respond less well, especially if there is neutropenia secondary to chemotherapy. Also these variables may increase the baseline risk of infection, which may then remain unmodified by immunoglobulin replacement therapy. When considering immunoglobulin replacement therapy in someone with recent infection, antecedent events such as chemotherapy and type of infection (non-encapsulated bacteria) may suggest that infection was not related to hypogammaglobulinaemia and therefore replacement immunoglobulin may not be indicated.

Practice varies internationally with respect to the use of immunoglobulin replacement in haematological malignancies and guidelines are sparse. This most likely reflects the limited evidence available. The majority of studies explore the use of IRT in CLL and MM rather than lymphoma or acute leukaemias.

Twelve randomised-controlled studies on efficacy of intravenous immunoglobulin therapy (IVIg) have been identified.[7-18] These studies were conducted between 1984 and 1994 predating the use of drugs such as rituximab which is likely to have an additional effect on B cells. The studies are limited by small sample size (12-84 participants) and in general do not define a high risk group most likely to benefit. One exception is a study of patients with plateau phase myeloma described below. Only three studies have examined IVIg therapy in acute leukaemia (predominantly lymphoblastic),[16-18] the remaining studies being in CLL or multiple myeloma.[7-15] Two of these latter studies also included a few patients with low-grade B cell lymphoma.[12,15]

Treatment protocols for IVIg used in MM and CLL differed between the studies, but most subjects received IVIg at a dose of 0.4 g/kg every three to four weeks. Two small studies (34 and 36 patients each) compared a dose of 0.5 mg/kg to 0.25 mg/kg in CLL and found no difference in efficacy with respect to reduction in infections however they were

underpowered to demonstrate an effect.[10,11] If IRT is commenced, current recommendations for dose and route of delivery of Ig replacement for immune deficiency should be followed (see chapter 7). Use of subcutaneous Ig has been suggested in one small study to offer an alternative to IVIg.[19] The role of prophylactic antibiotics has not really been addressed except for a small study in MM (see below).[20]

Chronic lymphocytic leukaemia (CLL)

Description of the condition

Studies in CLL enrolled subjects due to either a significant history of infection or hypogammaglobulinaemia. Some subjects therefore had normal immunoglobulins. These studies demonstrated significantly reduced infection in the active IVIg arm compared to placebo or no treatment.[7,8,12,13] In the largest study (84 subjects), there were 23 infections in the IVIg treated versus 42 in the placebo group.[7] In the 57 patients who completed a year of therapy, there were 14 infections in the IVIg group versus 36 in the placebo group. The number of subjects who remained infection free did not differ significantly with 13 in the IVIg group versus 11 in the placebo group. Three people in each group died.[7]

Multiple chemotherapy regimens have been shown by multivariate analysis to be associated with the greatest risk of serious infection (OR 3.04 versus hypogammaglobulinaemia 1.24).[21] There is other evidence that the infection risk in CLL is greater with hypogammaglobulinaemia.[3-5] In addition there is evidence of impaired vaccine responses in CLL, however, prospective studies examining infection rate in those with poor vaccine responses as compared to those with normal responses are lacking.[3-6] No RCT performed subgroup analysis to investigate differential efficacy in different risk groups or assessed antibody response to vaccination. Hence, in CLL it is not known whether certain patients are more likely to benefit when compared to others.

The role of antibiotic prophylaxis has not been systematically explored in this condition, however, there has been a small trial in MM with promising results (see over).[20]

A recently published Canadian guideline recommends the prophylactic use of IVIg in adults with haematological malignancy "associated with hypogammaglobulinaemia or dysfunctional gammaglobulinaemia."[22] The British Committee for Standards in Haematology recommend immunoglobulin replacement in CLL patients with hypogammaglobulinaemia, recurrent bacterial infection and failure to respond to prophylactic antibiotics.[23]

Diagnostic features

A careful assessment of patients with CLL should include a detailed infection history. Specifically, a history of serious or recurrent bacterial infection is noteworthy. An assessment of humoral immunity by measuring immunoglobulins and response to antigens such as tetanus, diphtheria, haemophilus (protein antigens) and pneumococci (Pneumovax®) (polysaccharide antigens) may provide some indication of risk of infection. The stage of disease (for example advanced) and presence of other unmodifiable variables such as multi-agent chemotherapy and neutropenia need to be considered as IRT may be less efficacious under these circumstances.

When to commence treatment

Recurrent or serious bacterial infection in CLL associated with hypogammaglobulinaemia where other significant risk factors (neutropenia or multiple courses of chemotherapy) are felt not to be causative. Impaired vaccine responses will support the decision. Prophylactic antibiotics should be considered initially.

Duration of therapy

Treatment should be for a trial of a year in the first instance with annual assessment of efficacy thereafter.

Multiple Myeloma (MM)

Description of the condition

A prospective study in multiple myeloma highlighted that reduced non-paraprotein IgG and IgA levels and/or poor antibody response to exogenous antigens were associated with an increase in serious infections.[2] The largest study of prophylactic IRT in MM included 83 subjects in plateau-phase.[9] An infection history or immunoparesis was not a requirement for enrolment but a subgroup analysis was performed. A significant decrease in serious and/or recurrent infections was demonstrated. However this benefit was seen only in certain subgroups.

Subjects who had a poor response to polysaccharide pneumococcal vaccine benefited with a decrease in infections compared to those with a good IgG response. Also patients with relatively preserved bone marrow function (as assessed by platelet count and haemoglobin) had a reduced rate of infection compared to those with more advanced disease (low platelets or haemoglobin) who had no decrease in infection rates. This study did not look at the impact of baseline non-paraprotein IgG levels. Adverse events were more common (12% of infusions) in the IRT group compared to the controls (5% of infusions). Although the majority were mild this patient group does appear to be more susceptible as this rate is higher than in CLL (2.7% of infusions).[9]

A small study enrolling 57 subjects during early chemotherapy in MM compared prophylactic cotrimoxazole with no treatment. Although there was a 25% withdrawal from the treatment arm due to side effects, there was still a significant reduction in infection rate during the three month study duration in the cotrimoxazole treated group.[20]

A recently published Canadian guideline on immunoglobulin use in haematological conditions recommends the prophylactic use of IVIg in adults with haematological malignancy "associated with hypogammaglobulinaemia or dysfunctional gammaglobulinaemia."[22] In addition guidelines on the management of MM from the British Committee for Standards in Haematology recommend immunoglobulin replacement when there are recurrent infections during plateau phase.[24]

Diagnostic features

A careful assessment of patients with MM should include infection history looking specifically for a history of serious or recurrent bacterial infection. An assessment of humoral immunity by measuring immunoglobulins (excluding the paraprotein) and response to antigens such as tetanus, diphtheria, haemophilus (protein antigens) and Pneumococci (Pneumovax®) (polysaccharide antigens) may provide some indication of risk of infection. The stage of disease (eg advanced with low platelets or haemoglobin) and presence of other unmodifiable variables such as multi-agent chemotherapy and neutropenia need to be considered as IRT may be less efficacious under these circumstances.

When to commence treatment

Recurrent or serious bacterial infection in plateau phase MM associated with a reduced non-paraprotein IgG or IgA, poor response to pneumococcus and where other significant risk factors eg neutropenia or multiple courses of chemotherapy are felt not to be causative. Prophylactic antibiotics should be considered initially.

Duration of therapy

Treatment should be for a trial of a year in the first instance with annual assessment of efficacy thereafter.

Acute leukaemia

Description of the condition

Severe infection is often a complication of intensive chemotherapy for acute leukaemia. This is most often due to neutropenia but secondary hypogammaglobulinaemia may also contribute. Three studies of IVIg use in childhood acute (predominantly lymphoblastic) leukaemia were published between 1989 and 1994.[16-18] Two small studies (81 patients total) examined the effect of the addition of IVIg to the treatment of an acute infective episode.[16-18] Both studies demonstrated a significant decrease in fever duration and in one the number of febrile episodes was also less. One study containing 60 participants looked at prophylactic IVIg use with results suggesting fewer infections.[17]

These studies are very small and at least 14 years old; no clear recommendation for IRT can be made in this patient group.

Other leukaemias / lymphomas

There are a variety of opinions across consensus documents regarding the use of IRT in acute leukaemia and non-Hodgkins lymphoma reflecting the lack of data. IRT may be considered in rare patients where there is recurrent severe bacterial infection and profound hypogammaglobulinaemia, and other causes of recurrent infection (eg neutropenia and advanced disease) are excluded.

Infection with Human Immunodeficiency Virus (HIV)

Paediatric HIV infection

Description of the condition

Children presenting with recurrent bacterial infections due to infection with HIV.

Diagnostic features

Children aged 12 years or younger with frequent, serious bacterial infections despite combination antiretroviral therapy (ART) and antibiotic therapy.

When to commence treatment

There is evidence to support the use of IRT for HIV infection in children in the absence of combination antiretroviral therapy (ART). However it is not clear that IVIg provides benefit not achievable with antibiotic prophylaxis. Since the advent of combination ART, morbidity and mortality from bacterial and opportunistic infections in HIV has decreased dramatically. There are no studies assessing the benefits of IRT in children with HIV infection who are treated with combination antiretroviral therapy.

Therefore, IVIg treatment for this condition would be uncommon and priority must be given to antiretroviral therapy. However, in exceptional patients who continue to experience recurrent bacterial infections despite adequate ART and prophylactic antibiotics, IVIg therapy can be considered.

Duration of therapy

Treatment should be for a trial of 1 year followed by cessation and repeat immunological evaluation (six months post cessation) prior to recommencement of therapy.

Adult HIV infection

IRT is not indicated, with or without combination antiretroviral therapy.

Congenital Rubella

Congenital rubella infection may be associated with persistent abnormalities of immunoglobulin production, which on occasion have required immunoglobulin replacement therapy. This is not generally seen with postnatal rubella infection.

Drug induced immunodeficiency

Description of the condition

Reduced levels of serum immunoglobulins may be induced by a large number of immunosuppressive therapeutic strategies or as an idiosyncratic reaction to some drugs (table 2). In some cases there may be associated functional antibody defect and/or recurrent bacterial infections. The antibody defect may not be reversible upon cessation of the drug.

B cell depleting therapies require special consideration

Rituximab is an anti-CD20 monoclonal antibody that selectively depletes B cells from the pre-B stage to the mature B stage but does not affect hematopoietic stem cells or plasma cells. Single treatment courses of rituximab do not generally induce deficiencies in total serum Ig concentrations or antibody-specific IgG.[25] Despite depletion of circulating B cells for 6-12 months following therapy there is usually no resultant significant hypogammaglobulimaemia and IVIg replacement therapy is generally not necessary. Repeated courses may induce more prolonged hypogammaglobulinaemia for up to nine months.[26, 27]

When to commence treatment

Wherever possible the drug should be ceased, reduced in dose or changed to an alternative drug. Prophylactic antibiotics should be considered as a first option. IRT may be considered in rare cases, where patients present with recurrent bacterial infections due to drug induced humoral immunodeficiency (most commonly secondary to immunosuppressive agents) where the inciting drug cannot be reduced or ceased without substantial morbidity. Other causes for infection eg neutropenia should be excluded, and specific antibody responses to antigens may assist in the decision to commence immunoglobulin replacement therapy. Immunoglobulin replacement therapy is not indicated in patients who are not experiencing clinical infections.

Duration of therapy

Duration will depend upon the clinical setting.

Post transplantation

Description of the condition

Patients undergoing both haemopoietic stem cell transplantation (HSCT) and solid organ transplantation are at risk of developing infections due to immunosuppression

Table 2. Drug induced antibody deficiency

Idiosyncratic effects	Agents with known immunosuppressive effects
• Antimalarial agents • Captopril • Fenclofenac • Gold salts • Penicillamine • Carbamazepine • Phenytoin • Sulfasalazine	• Glucocorticosteroids • Cytotoxic immunosuppressives • Cancer chemotherapy • B cell depleting monoclonals eg rituximab (see text) • Combination transplant rejection regimens

from pre-transplant preparative agents, graft-versus-host disease, and delayed immunocompetence during post-engraftment period. Cytomegalovirus (CMV) is a significant cause of morbidity and mortality following transplantation, especially in children, who are at risk of primary infection. The provision of antibody may prevent or treat infections.

Specific products available that may be considered for use include intravenous immunoglobulin and CMV hyperimmune globulin (CMVIg). CMV hyperimmune globulin has an approximately 5-8 fold enrichment in anti-CMV titre compared with IVIg.[28] Its therapeutic use has become less important with the availability of potent antiviral drugs.

The use of IVIg and CMVIg in the setting of prevention of infections post-transplantation is still a matter of controversy despite numerous trials.[29, 31] Many of the trials have produced contradictory results, findings that were not statistically significant, or were not blinded or randomized. None of the trials were placebo controlled, and most were carried out before recent advances in transplants, such as effective drugs for CMV infection, were available. In summary, results from these studies were conflicting, with some studies showing benefit from higher-dose IVIg, others showing no significant difference in effect between 2 or 3 different doses of IVIg.

Both IVIg and CMVIg have been used to treat CMV infection but no formal comparison between the two products has been made. There is no difference in incidence of CMV infection in patients receiving prophylactic standard IVIg (400 mg/kg/week) as compared to CMVIg (100 mg/kg/week).[32] The main disadvantage of CMVIg is the high cost (35% more expensive than IVIg).

When to commence treatment

- There is no proven benefit from prophylactic IVIg in preventing bacterial infections in patients undergoing HSCT. [33, 35]
- There is no proven benefit from prophylactic IVIg in preventing late infections in patients undergoing HSCT in non-immunodeficient patients
- There is no proven benefit from prophylactic IVIg in preventing RSV infections in patients undergoing HSCT
- Some multinational protocols for HSCT recommend routine use of IVIg for hypogammaglobulinaemia - IVIg may be administered to comply with protocol recommendations but the benefit of this approach has not been adequately studied and there is considerable uncertainty as to the efficacy of such an approach. [36]
- IRT may be considered for acquired hypogammaglobulinaemia post allogeneic HSCT or Solid Organ Transplantation and:
    - a recent episode of a severe invasive infection, which is reasonably thought to be caused by low levels of IgG; or

- recurrent episodes of clinically significant infections (eg, pneumonia), which are reasonably thought to be caused by low levels of IgG.

- The use of IVIg and CMVIg enriched preparations in the prevention and management of CMV infections remains controversial:
  - currently there is no indication for CMVIg or IVIg in the prophylaxis of CMV disease in recipients of solid organ transplants as it does not significantly reduce CMV disease and CMV-associated mortality in solid organ transplant recipients.[37]
  - although there are cited reports that have supported the use of IVIg and CMVIg in the prophylaxis of CMV disease in patients undergoing HSCT, there are doubts regarding efficacy and recommendations for routine use have no clear basis
  - although there are randomized control studies demonstrating pre-emptive gancyclovir to be highly effective, there is no evidence to suggest that the addition of IVIg or CMVIg increases efficacy[37]
  - although there are studies suggesting benefits from a combination of IVIg or CMVIg and ganciclovir in the treatment of interstitial CMV pneumonitis, this area is unresolved.[38, 41]

Larger doses of IVIg might need to be used because of the shortened half-life of immunoglobulin in HSCT patients. The half-life is estimated to be six days.[42] The authors were unable to provide an explanation for the reduced half-life of IgG in these patients but suggested that weekly IVIg is likely to be optimal in this population. It has been postulated that the reduced half-life could be secondary to increased protein catabolism and/or acute graft-versus host disease.[31] In one of the largest studies, 500 mg/kg body weight was given weekly until day 90, then monthly until day 360 after transplantation.[43] Further research is required to determine dose, frequency, and duration of administration of IVIg in view of limited evidence.

Protein losing states

Protein losing states include protein losing enteropathy, lymphangiectasia, nephrotic syndrome, chylothorax, and patients with severe burns. In general protein losing states encompass a group of disorders in which routine use of immunoglobulin replacement therapy is not recommended. The typical antibody profile seen in protein losing states is of reduced serum IgG with preservation of IgA and IgM due to their respective rates of production. Lymphopenia may be a feature where there are structural abnormalities of the lymphatics such as in intestinal lymphangiectasia and chylothorax.

As the functional antibody response remains intact increased susceptibility to infection is uncommon in these conditions. Rarely, intestinal lymphangiectasia may be associated with reversed CD4:CD8 ratio[43] and reduced antibody synthesis (functional antibody response), in which case IRT may be indicated.

Use of IVIg will raise IgG levels only transiently and is therefore not generally recommended. IRT may be considered in patients with prolonged hypogammaglobulinaemia, very low IgG eg <2 g/l or defective functional antibody responses who experience recurrent infection despite antibiotic prophylaxis. In this situation there may be added benefit of the subcutaneous route of immunoglobulin administration because of delayed release of IgG into serum.

Prematurity

Maternal transfer of immunoglobulin to the fetus occurs as early as 17 weeks of gestation and progressively increases until birth. Maternal levels are reached around 33 weeks gestation. The endogenous synthesis of IgG occurs soon after birth while levels of maternal derived IgG decrease. At about 2 months, circulating IgG synthesised by the infant equals the amount derived by placental transfer and the level of serum IgG is lowest between 2-4 months of age. By 10-12 months the serum IgG is completely derived from the infant. The premature infant has a lower IgG concentration level at birth[45] than healthy term infants however it is unclear how much this contributes to the increased risk of infection in the perinatal period.

IVIg for prevention of infection in preterm infants

Studies do not support the routine use of IVIg as prophylaxis against infection in preterm or low birth weight babies.[46] A Cochrane meta-analysis of 19 studies which included approximately 5,000 preterm and / or LBW infants found a small but statistically significant 3% reduction in sepsis and a 4% reduction in serious infections which are considered to be of marginal clinical significance. There was no reduction in mortality from infection or any other cause, and other important outcomes such as necrotizing

enterocolitis, intraventricular haemorrhage, or length of hospital stay.[46]

IVIg for the treatment of sepsis in preterm neonates

A Cochrane review (updated 2008) [47] of six randomized studies (n=318) examined the effect of IVIg treatment on mortality in newborn infants <28 days of age with clinically suspected infections. IVIg therapy was associated with a reduced mortality of borderline statistical significance [RR 0.63 (95% CI 0.40, 1.00)]. Study subjects included both preterm and term neonates. The authors concluded that there is currently insufficient evidence to support the routine administration of IVIg preparations for the prevention of mortality from suspected or subsequently proven neonatal infections.[47, 48]

References

1. Fahey JL, Scoggins R, Utz JP, Szwed CF. Infection, antibody response and gamma globulin components in multiple myeloma and macroglobulinemia. Am J Med 1963;35:698-707.

2. Hargreaves RM, Lea JR, Griffiths H, Faux JA, Holt JM, Reid C, et al. Immunological factors and risk of infection in plateau phase myeloma. J Clin Pathol 1995;48(3):260-6.

3. Tsiodras S, Samonis G, Keating MJ, Kontoyiannis DP. Infection and immunity in chronic lymphocytic leukaemia. Mayo Clin Proc 2000;75(10):1039-54.

4. Chapel HM, Bunch C. Mechanisms of infection in chronic lymphocytic leukemia. Semin Hematol 1987;24(4):291-6.

5. Morrison VA. The infectious complications of chronic lymphocytic leukemia. Semin Oncol 1998;25(1):98-106.

6. Sinisalo M, Aittoniemi J, Kayhty H, Vilpo J. Vaccination against infections in chronic lymphocytic leukemia. Leuk Lymphoma 2003;44(4):649-52.

7. Cooperative Group for the study of immunoglobulin in Chronic Lymphocytic Leukaemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988;319(14):902-7.

8. Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol 1995;17(1):75-80.

9. Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet 1994;343(8905):1059-63.

10. Chapel H, Dicato M, Gamm H, Brennan V, Ries F, Bunch C, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol 1994;88(1):209-12.

11. Gamm H, Huber C, Chapel H, Lee M, Ries F, Dicato MA. Intravenous immune globulin in chronic lymphocytic leukaemia. Clin Exp Immunol 1994;97 Suppl 1:17-20.

12. Griffiths H, Brennan V, Lea J, Bunch C, Lee M, Chapel H. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood 1989;73(2):366-8.

13. Molica S, Musto P, Chiurazzi F, Specchia G, Brugiatelli M, Cicoira L, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica 1996;81(2):121-6.

14. Hargreaves RM LJ, Holt J, et al. Infection, immune responses and IV immunoglobulin prophylaxis in myeloma (abstract). Br J of Cancer 1992;66:261.

15. Schedel I. Intravenous immunoglobulin replacement in secondary antibody deficiency syndrome. [German]. Diagnostik & Intensivtherapie 1982;7(10):254-63.

16. Gebauer E, Tomi J, Stevanovi S. [Intravenous immunoglobulin in the treatment of infections in children with acute leukemias]. Medicinski Pregled 1994;47(1-2):52-5.

17. Gimesi A, Eibl M, Koos R, Somlo P, Magyarossy E, Kardos G, et al. Immunoglobulin prophylaxis during intensive treatment of acute lymphoblastic leukemia in children. Acta Paediatrica Hungarica 1992;32(2):115-25.

18. Sumer T, Abumelha A, al-Mulhim I, al-Fadil M. Treatment of fever and neutropenia with antibiotics versus antibiotics plus intravenous gammaglobulin in childhood leukemia. Eur J Pediatr 1989;148(5):401-2.

19. Hammarstrom L, Samuelsson J, Grimfors G. Subcutaneous gammaglobulin for patients with secondary hypogammaglobulinaemia. Lancet 1995;345(8946):382-3.

20. Oken MM, Pomeroy C, Weisdorf D, Bennett JM. Prophylactic antibiotics for the prevention of early infection in multiple myeloma. Am J Med 1996;100:624-8.

21. Molteni A, Nosari A, Montillo M, Cafro A, Klersy C, Morra E. Multiple lines of chemotherapy are the main risk factor for severe infections in patients with chronic lymphocytic leukemia with febrile episodes. Haematologica 2005;90(8):1145-7.

22. Anderson D, Ali K, Blanchette V, Brouwers M, Couban S, Radmoor P, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfusion Med Rev 2007;21(2 Suppl 1):S9-S56.

23. Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, et al. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol 2004;125(3):294-317.

24. Smith A, Wisloff F, Samson D, Forum UKM. Nordic Myeloma Study G, British Committee for Standards in H. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol 2006;132(4):410-51.

25. Vallerskog T, Gunnarsson I, Widhe M, Risselada A, Klareskog L, van Vollenhoven R, et al. Treatment with rituximab affects both the cellular and the humoral arm of the immune system in patients with SLE. Clin Immunol 2007;122(1):62-74.

26. Quartier P, Brethon B, Philippet P, Landman-Parker J, Le Deist F, Fischer A. Treatment of childhood autoimmune haemolytic anaemia with rituximab. Lancet 2001;358(9292):1511-3.

27. Rao A, Kelly M, Musselman M, Ramadas J, Wilson D, Grossman W, et al. Safety, efficacy, and immune reconstitution after rituximab therapy in pediatric patients with chronic or refractory hematologic autoimmune cytopenias. Pediatr Blood Cancer 2008;50(4):822-5.

28. Snydman DR, McIver J, Leszczynski J, Cho SI, Werner BG, Berardi VP, et al. A pilot trial of a novel cytomegalovirus immune globulin in renal transplant recipients. Transplantation 1984;38:553-7.

29. Glowacki LS, Smaill FM. Use of immune globulin to prevent symptomatic cytomegalovirus disease in transplant recipients--a meta-analysis. Clin Transplant 1994;8(1):10-8.

30. Guglielmo BJ, Wong-Beringer A, Linker CA. Immune globulin therapy in allogeneic Bone Marrow Transplant: a critical review 1994;13:499-510.

31. Sokos DR, Berger M, Lazarus HM. Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2002;8(3):117-30.

32. Zikos P VLM, Lamparelli T. A randomised trial of high dose polyvalent intravenous immunoglobulin (HDIgG) vs. Cytomegalovirus (CMV) hyperimmune IgG in allogenic hematopoietic stem cell transplants (HSCT). Haematologica 1998;83:132-7.

33. Cordonnier C C, S, Legrand M, Dhedin N. Should Immunoglobulin Therapy Be Used in Allogeneic Stem-Cell Transplantation? A Randomized, Double-Blind, Dose Effect, Placebo-Controlled, Multicenter Trial. Ann Intern Med 2003;139:8-18.

34. Winston DJ AJ, Wolff SN. A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. Bone Marrow Transplant 2001;28:187-96.

35. Wolff SN, Fay JW, Herzig RH, Greer JP, Dummer S, Brown RA, et al. High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med 1993;118:937-42.

36. Robinson P, Anderson D, Brouwers M, Feasby TE, Hume H. Evidence-based guidelines on the use of intravenous immune globulin for hematologic and neurologic conditions. Transfus Med Rev 2007;21(S1):S3-8.

37. Hodson EM, Jones CA, Strippoli GF, Webster AC, Craig JC. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev 2007;2:CD005129.

38. Laver J. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. Ann Intern Med 1988;109:777-82.

39. Ljungman P, Englhard D, Link H, Biron P, Brandt L, Brunet S, Cordonnier C, et al. Treatment of interstitial pneumonitis due to cytomegalovirus with ganciclovir and intravenous immune globulin: experience of European Bone Marrow Transplant Group. Clin Infect Dis 1992;14:831-5.

40. Winston DJ, Ho WG, Rasmussen LE, Lin CH, Chu CL, Merigan TC, et al. Use of intravenous immune globulin in patients receiving bone marrow transplants. J Clin Immunol 1982;2: S42-7.

41. Bueno J, Ramil C, Green M. Current management strategies for the prevention and treatment of cytomegalovirus infection in pediatric transplant recipients. Paediatric Drugs 2002;4:279-90.

42. Rand KH Gibbs K, Derendorf H, Graham-Pole J. Pharmacokinetics of intravenous immunoglobulin (Gammagard) in bone marrow transplant patients. J Clin Pharmacol 1991;31(12):1151-4.

43. Sullivan KM, Kopecky KJ, Jocom J, Fisher L, Buckner CD, Meyers JD, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 1990;323:705-9.

44. Fuss IJ, Strober W, Cuccherini BA, Pearlstein GR, Bossuyt X, Brown M, et al. Intestinal lymphangiectasia, a disease characterized by selective loss of naive CD45RA+ lymphocytes into the gastrointestinal tract. Eur J Immunol 1998;28(12):4275-85.

45. Lewis, DB, Wenwei, Tu. Physiologic immunodeficiency of immaturity. In: Steihm ER OH, Winklestein JA, editor. Immunologic Disorders in Infants and Children 5th ed: Saunders 2004;722-6.

46. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Cochrane Database Syst Rev [serial on the Internet] 2004;(1):CD000361.

47. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database Syst Rev [serial on the Internet] 2004;(1):CD001239.

48. Suri M, Harrison L, Van de Ven C, Cairo MS. Immunotherapy in the prophylaxis and treatment of neonatal sepsis. Curr Opin Pediatr 2003;15(2):155-60.

Chapter 7

Approach to immunoglobulin replacement

- An initial maintenance dose would be 0.4-0.6g/kg per month
- Immunoglobulin replacement can be given via intravenous or subcutaneous routes
- Dose adjustments are made using a combination of clinical parameters and trough levels
- Trough levels should be maintained above the lower limit of normal age related reference ranges or above 5g/L in children, whichever is greater
- Higher doses of immunoglobulin may provide better protection from infection in some individuals

Immunoglobulin replacement in immune deficient patients can be achieved with either intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg). Once it is determined that a patient requires immunoglobulin replacement, decisions to be made about replacement for any patient will include:

1. Route: There are many IVIg products licensed worldwide,[1] with some products readily available for intravenous use in the Asia Pacific region (Table 1) and few products currently available for subcutaneous use (Table 2).
2. Dose
3. Location for infusions: home versus hospital
4. Indications for dose adjustment.

Prior to starting therapy, patients and their families will need information about the range of replacement products available for use. Written informed consent should ideally be obtained and is a requirement in some centres. If IRT is to be used for a trial period, it is essential to discuss the anticipated duration of IRT and expected outcomes in advance of commencement. Prior to commencement of immunoglobulin replacement, baseline investigations should be arranged (see chapter 8) including renal and liver function. Before the first infusion it is advisable to store serum in case there is subsequent need to determine presence or absence of a specific infection at the time of starting treatment. Saving specimens may also be considered on a regular basis during immunoglobulin replacement therapy (see chapter 8).

Intravenous versus subcutaneous immunoglobulin replacement

The decision on which route of administration is best for a given patient will depend on various factors including availability of appropriate products, patient factors, patient preference, and cost. There are advantages and disadvantages to each approach (Table 3) and the preferred route, and consequently infusion frequency, may vary at different times during a given patient's life.

Other medical conditions will influence the decision to proceed with either IVIg or SCIg replacement. Subcutaneous treatment may be contraindicated in severe thrombocytopenia, bleeding disorders,

or in those on anticoagulation therapy. It may be problematic for patients with widespread eczema. Subcutaneous treatment may be preferred if there are side effects from IV replacement or where IV access is difficult. Age is a factor in making the decision, with less frequent procedures often preferred in children, though SCIg has been shown to be well tolerated in infants and young children.[2] Subcutaneous Immunoglobulin can be infused at various sites, with the abdomen being the most common. Infusion into the thigh is also possible. Limited subcutaneous tissue may limit site options for infusion. Availability of suitable product has previously been a significant factor limiting the use of SCIg replacement therapy, though there are an increasing number of products becoming available for subcutaneous use. There is published evidence [3] that intravenous products can also be given safely by the subcutaneous route.

In terms of outcomes such as the IgG level achieved or the control of recurrent infections, there is no data to suggest advantage with use of either the IV or SC routes although long term studies are not available. A multicentre comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy showed no significant differences in rates of breakthrough infections or adverse reactions. The IgG levels achieved were equivalent for the IV and SC replacement groups.[4]

Table 1 Asia Pacific intravenous immunoglobulin products

Product	Form	$T^{1/2}$ in PID patients	Refrigeration	Filter	IgA	Excipient
Intragam® P	6% solution	39.7 days	Yes or use within three months if removed and stored below 25°C	No	<0.025mg/ml	10% maltose
Gammagard® Liquid	10% solution	35 days	No	No	37 mcg/ml	Glycine
Octagam®	5% solution	40 days	Yes (may also be stored at room temp to max of 25°C for 24 months)	No	<0.2mg/ml	10% maltose
Sandoglobulin®	Lyophilized. Intravenous administration as a solution depending on volume of diluent	41.5 days	No (stored below 25°C protected from light)	Yes	Maximum 40mg/g protein	Sucrose
Sandoglobulin® NF Liquid	12% solution	34 days	Yes	No	<0.1mg/ml (normally below 0.015mg/ml)	L-proline L-isoleucine Nicotinamide

Practical aspects of IVIg replacement

On initiation of IVIg replacement therapy, a loading dose may be considered, with 1g/kg given either as a single dose or as several smaller doses over a few days. Doses should be rounded to the nearest amount contained within a vial rather than discarding IVIg. The half life of naturally occurring IgG in the normal host is approximately 21-28 days. There are various half lives quoted for different IVIg products (Table 1).

Maintenance doses are generally commenced at 0.4-0.6g/kg given each 3-4 weeks, and again doses should be rounded to finish each vial rather than discard IVIg. A higher maintenance dose of 0.6g/kg/4 weeks in adults and 0.8g/kg/4 weeks in children has been shown to reduce number (3.5 vs 2.5 per patient) and duration (33 vs 21 days) of infections amongst XLA and CVIDs patients.[5] For some patients, particularly those on home IVIg therapy, more frequent infusions may be more convenient and are an acceptable alternative, with the same cumulative dose per month administered.

Use of topical analgesia prior to obtaining venous access should be considered, particularly in children. Options include local anaesthetic creams such as prilocaine and lignocaine (EMLA®; effective after 30-40 minutes), amethocaine (Ametop®; effective after 20-30 minutes), or the coolant spray ethyl chloride (effective immediately).

Each IVIg product has product information with suggested infusion rates, usually advising to commence each infusion slowly and increasing as tolerated. Most IVIg infusions will take 2-4 hours to complete. The Intragam® P data sheet suggests a starting rate of 1ml/minute, increasing each 15 minutes to 4ml/minute maximum, with no modification suggested for weight, however slower rates should be used in infants and young children. Other published recommendations include starting each infusion at 0.5-1mg/kg/min increasing to a maximum of 4mg/kg/minute,[1] with one study suggesting that rates of over 15mg/kg/min[6] can be tolerated by selected patients.

Prior to starting each infusion, baseline recordings of heart rate, respiratory rate, blood pressure and temperature should be recorded, with repeat recordings if required. The batch numbers of IVIg product used during each infusion must be noted in the patient's records to enable retrospective verification in the event of transmitted infection.

IVIg infusions have been shown to be sufficiently safe to enable patients (adults and children) to receive infusions at home, with the help of a responsible adult. Home therapy is an option for patients established on IVIg who are not having infusion reactions. Therapy cannot be initiated at home because of the increased frequency of adverse reactions. In one large study of 290 patients

Table 2 Asia Pacific intramuscular and subcutaneous immunoglobulin products

Product	**Form**	**IgA**	**Excipient**	**Indicated for IgG replacement in PID**	
				IM use	**SC use**
Gammanorm®	16.5% solution	<0.082mg/ml	Glycine	Yes	Yes
Normal Immunoglobulin-VF	16% solution	Not available	Glycine	Yes	No
Subgam®	14-18% solution	Max 0.2% w/w of total protein	Glycine	Yes	Yes

receiving infusions at home (9474 infusions), there were a total of 87 reactions, 72 of which were mild and 15 classified as moderate; there were no serious reactions.[7]

Home therapy requires careful selection of patients in terms of patient reliability and ability to learn the techniques for venepuncture, IV infusion and aseptic technique. Formal education as to the nature and management of adverse reactions is needed and a log of adverse reactions should be established and maintained (Appendix 1). Resources including IVIg, pumps and monitoring equipment are required, as is the ongoing support and supervision of the supervising clinician / immunologist. Self injectable adrenaline was initially recommended for patients self infusing IVIg at home, but recent data from a large study found that this is unnecessary given the reported safety of home infusions.[7]

Practical aspects of SCIg replacement

Subcutaneous infusions of immunoglobulin (SCIg) are an alternative to IVIg replacement therapy, with the same cumulative dose of immunoglobulin given each month. Use of a higher monthly replacement dose, to maintain equivalent area under the curve for serum IgG over time, has been considered.[8] While this resulted in a higher serum IgG level than when a dose equivalent to the IV dose was used, there was no apparent benefit in terms of infection control.

The regimen for SCIg infusions can be tailored to the patient and allows considerable flexibility, with divided doses given on average every 3-7 days, at 1-2 sites per infusion. Steady state is reached after six months with weekly subcutaneous infusions or after 1 week if the patient is given daily infusions for five consecutive days; thereafter, steady state can be maintained with weekly infusions.[8] For newly diagnosed patients with very low IgG being commenced on immunoglobulin replacement therapy, loading doses of either intravenous or subcutaneous immunoglobulin should be considered prior to starting SCIg, as this may help achieve normal levels more rapidly.[2]

Subcutaneous immunoglobulin replacement is usually home based therapy. The treatments are given by subcutaneous infusion via a battery powered pump, most often into the abdominal wall, with the thigh or arm as possible alternative sites, depending on adequate subcutaneous tissue. Various rates

Table 3 Comparison of Strengths and Weaknesses of IVIg and SCIg

Therapy	Strengths	Weaknesses
IVIg	• Less frequent infusion (q3-4 week) • Rapid increase in serum IgG	• Usually hospital based • Intravenous access required • Risk immediate adverse effects
SCIg	• Home based therapy • IV access not needed • Few systemic side effects; can be used for patients with previous reactions to IVIg • Improved Quality of Life of patient and family with flexibility, independence, and empowerment • Reduced cost of treatment – hospital costs and patient time	• Frequency of dosing will depend upon the dose to be administered, volume that the patient is able to tolerate per infusion and patient preference • Local side effects (swelling, induration, local inflammation, itch) • Requirement of a pump or pumps

of infusion have been published; rates of 20ml/hr have been tolerated in children [2] and rates of up to 40ml/hr have been tolerated in adults.[9] The volume able to be infused at any site may be up to 20-30ml as tolerated.[10] SCIg infusions are generally well tolerated. There is often erythema and swelling at the site during the first few infusions, but these local reactions subside rapidly and rarely recur after 10 or so infusions. Given the demonstrated safety of SCIg infusions, provision of self injected adrenaline is not necessary.[11]

As with home IVIg, selection of patients for SCIg therapy needs to take into account the ability of the patient or family to reliably administer the treatment. Depending on the product used, patients may also require the facility to store the SCIg product at 4°C. Arrangements for how to manage infusions during illness or vacation need to be discussed. Patients need to keep a log of any adverse reactions to SCIg (Appendix 1), with an organized system whereby adverse reactions are reported to the supervising physician.

Whether immunoglobulin replacement is with IVIg or SCIg, the possibility of home based therapy should be considered, with improved quality of life demonstrated, particularly with SCIg.[12]

Immunoglobulin replacement dose adjustment

After initiation of IVIg therapy the blood level of IgG increases rapidly and stabilizes over 3-4 months as the tissue spaces become saturated with IVIg. Similarly after initiation of SCIg the blood level of IgG rises over the next 3-6 months, even without a loading dose of IVIg.[10] Ongoing dose adequacy is then assessed primarily by considering clinical progress of the patient and control of recurrent infections. The replacement dose in g/kg/month, and the pre-infusion trough IgG (in IVIg) or steady state IgG (in SCIg) achieved are also used to assess dose adequacy.

Prior to the development of IVIg replacement therapy, doses were limited by the volume that could be administered by intramuscular IgG injection, and relatively low serum trough IgG levels were achieved. With the availability of IVIg preparations, higher replacement doses are able to be administered and higher trough levels of IgG achieved. Early studies comparing intramuscular or low dose IV immunoglobulin replacement with higher dose IVIg showed higher trough IgG and a reduction in intercurrent infections with higher dose IVIg replacement.[13,14] One early study suggested that doses of IVIg achieving a trough of >5g/L were associated with a reduction in acute infection.[15]

The relationship between trough IgG levels, monthly dose of IVIg and clinical outcome is summarised in Table 4. Some data suggests that the trough IgG at which infections are prevented may vary between patients, between IVIg products, and may depend on associated clinical problems (such as chronic lung disease).[16,17] Trough levels should be maintained within the normal age related reference range.

Progression of pulmonary disease has been shown to occur despite a trough IgG level of >5g/L in a group of Finnish patients with CVIDs and XLA.[18] A level of at least 6g/L was associated with prevention of progression of pulmonary disease in adult patients with CVIDs.[19] Residual serum IgG levels of >8g/L compared to levels of 5-8g/L further reduced the risk of severe bacterial infection (pneumonia, septicemia and cellulitis) in children with XLA.[20] In a double-blind randomized cross over study [5] of two doses of IVIg (0.3g/kg/4 weeks versus 0.6 g/kg/4 weeks in adults and 0.4g/kg/4 weeks versus 0.8 g/kg/4 weeks in children), the higher doses of IVIg were associated with a reduced number and duration of infections. The trough IgG increased from 6.3g/L to 9.4g/L on high dose treatment. Another study [16] compared two IVIg products. Infection rates were lower in those receiving replacement doses of >0.4g/kg/dose, with reduced infection rates reported with higher trough IgG, and the best protection observed in those with trough IgG of >9g/L. There are no data suggesting that levels beyond this confer further protection, and consideration of down titration of immunoglobulin replacement dose should be considered if very high trough or steady state IgG levels are being achieved.

The trough IgG will not be useful in determining dose adequacy in patients who commenced immunoglobulin replacement with normal serum IgG levels and poor specific antibody production, and clinical parameters will be the most important outcome measure in determining dose.[1]

Dose adjustment may be achieved either by increasing the dose of immunoglobulin given, or by shortening the interval between immunoglobulin doses. Currently there are no studies indicating which of these approaches is a more effective strategy. The decision will be influenced by current dose and route, as well as patient preference.

Table 4 Relationship between trough IgG, dose and clinical outcome

Author	Patients	Dose	Trough IgG	Outcome
Eijkhout [5]	N=43 Adults and children XLA and CVID	Cross over 0.3 vs. 0.6g/kg/4 weeks for adults 0.4-0.8 g/kg/4 weeks for children	Mean 9.4g/L (high dose) Mean 6.6g/L (low dose)	Reduced numbers of infections on high cf low dose Significantly increased trough IgG on high cf low dose
Liese [21]	N=29 Children XLA	>0.4 g/kg/3 weeks vs. 0.2 g/kg/3 weeks	Mean 6.5g/Lvs. Mean 2.2g/L	Reduced episodes pneumonia on high vs low dose Reduced days hospitalisation on high vs low dose
Quartier [20]	N=35 Children XLA	0.26-1.12g/kg/3 weeks	Median 5.5g/L	Trough level of 5g/L associated with prevention of acute bacterial infection Level of >8g/L amoliated with further reduction in risk of acute bacterial infection
Roifman [15]	N=12 Adults and children XLA and CVIDs Chronic lung disease	0.6 g/kg/4 weeks vs. 0.2 g/kg/4 weeks		Reduced numbers of acute infections during periods with trough IgG of >5g/L
Roifman [16]	N=146 Adults and children Various PID diagnoses Comparison of two IVIg products	0.1-0.6 g/kg/3-4 weeks		Fewer validated infections in patients on >0.4 g/kg/4 weeks Fewer validated infections in patients with trough IgG 7-9g/L cf <7g/L Further reduction in infections with trough IgG >9g/L Apparent difference in efficacy between two IVIg products in terms of reduction in infection

References

1. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006;117(4 Suppl):S525-53.
2. Gaspar J GB, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Arch Dis Child 1998;79(1):48-51.
3. Stiehm ER, Casillas AM, Finkelstein JZ, Gallagher KT, Groncy PM, Kobayashi RH, et al. Slow subcutaneous human intravenous immunoglobulin in the treatment of antibody immunodeficiency: use of an old method with a new product. J Allergy Clin Immunol. 1998;101(6 Pt 1):848-9.
4. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000;20(2):94-100.
5. Eijkhout HW, van Der Meer JW, Kallenberg CG, Weening RS, van Dissel JT, Sanders LA, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. Ann Internal Med 2001;135(3):165-74.
6. Schiff RI, Schiff SD, Buckley RH. Rapid infusion of Sandoglobulin in patients with primary humoral immunodeficiency. J Allergy Clin Immunol 1991;88(1):61-7.
7. Brennan VM, Salome-Bentley NJ, Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol. 2003;133(2):247-51.
8. Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol 2006;26(3):265-73.
9. Thomas MJ BV, Chapel HH. Rapid subcutaneous immunoglobulin infusions in children. Lancet 1993;342(8884):1432-2.
10. Gardulf A, Hammarstrom L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet 1991;338(8760):162-6.
11. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. Pediatr 1996;98(6 Pt 1):1127-31.
12. Gardulf A, Nicolay U. Replacement IgG therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies. Curr Opin Allergy Clin Immunol 2006;6(6):434-42.
13. Cunningham-Rundles C, Siegal FP, Smithwick EM, Lion-Boule A, Cunningham-Rundles S, O'Malley J, et al. Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. Ann Internal Med 1984;101(4):435-9.

14. Garbett ND, Currie DC, Cole PJ. Comparison of the clinical efficacy and safety of an intramuscular and an intravenous immunoglobulin preparation for replacement therapy in idiopathic adult onset panhypogammaglobulinaemia. Clin Exp Immunol 1989;76(1):1-7.

15. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet 1987;1(8541):1075-7.

16. Roifman CM, Schroeder H, Berger M, Sorensen R, Ballow M, Buckley RH, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency. A randomized double-blind trial. Int Immunopharmacol 2003;3(9):1325-33.

17. Chapel H, Brennan V, Delson E. Immunoglobulin replacement therapy by self-infusion at home. Clin Exp Immunol 1988;73(1):160-2.

18. Kainulainen L, Varpula M, Liippo K, Svedstrom E, Nikoskelainen J, Ruuskanen O. Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 1999;104(5):1031-6.

19. de Gracia J, Vendrell M, Alvarez A, Pallisa E, Rodrigo MJ, de la Rosa D, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. Int Immunopharmacology 2004;4(6):745-53.

20. Quartier P, Debre M, De Blic J, de Sauverzac R, Sayegh N, Jabado N, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr 1999;134(5):589-96.

21. Liese JG, Wintergerst U, Tympner KD, Belohradsky BH. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. Am J Dis Child (1960) 1992;146(3):335-9.

Chapter 8

Ongoing care of patients receiving immunoglobulin replacement therapy

- Patients on Immunoglobulin Replacement Therapy (IRT) should have regular (3-6 monthly) review by their treating physician to determine current clinical status and the development of new morbidities
- Routine Chest CT is not recommended in children due to the increased lifetime risk of cancer
- A multidisciplinary approach (including physiotherapy) to patient management is desirable
- The main infectious complications in patients on IRT involve the sinopulmonary tract and may lead to bronchiectasis
- Continuous prophylactic antibiotics may be required when recurrent infections occur despite optimal IRT
- In some conditions a trial of IRT for 12-24 months may be initiated following which IRT cessation and immunological re-evaluation is required

Monitoring Of Patients On Immunoglobulin Replacement Therapy (IRT)

Clinical review should occur routinely in all patients on IRT at a frequency that is dictated by clinical status. In general, review should take place at 3-6 monthly intervals, however, the capacity for early review in the case of intercurrent illness is essential. It is important that this evaluation is conducted by a clinical immunologist with training and experience in the care of patients with antibody deficiency. In addition, there should be a coordinated approach to care with involvement of a general practitioner/ paediatrican/physician to whom the patient can present for routine issues between review appointments with the clinical immunologist. At each review with the clinical immunologist, all patients are monitored to determine current clinical status and for the development of new morbidities.

Routine evaluation of all patients on IRT should include the following tests shown in Table 1 and may include the tests shown in Table 2.

Table 1.
Evaluation of patients on IRT

Test	**Interval**	**Potential Complication Being Assessed**
Full blood count (FBC)	3-6 Monthly	Anaemia Cytopaenias
Creatinine	3-6 Monthly	Renal failure – a rare complication of IVIg use (see Chapter 9 - adverse effects)
Liver function	3-6 Monthly	Abnormal LFTs can detect the possibility of blood borne viral infection where early diagnosis and treatment is beneficial [1, 2]
Trough IgG	3-6 Monthly	Refer to chapter 7 for discussion of IgG tough levels NB. Trough IgG levels are not a valid method of monitoring IRT in patients with Specific Antibody Deficiency (SAD) and IgG subclass deficiency
Height/Weight	At each visit for children and six-monthly for adults	To adjust the dose as indicated and to monitor general well being
Blood Pressure Measurement	At each visit	
Spirometry	Yearly or as indicated by respiratory status	To monitor for deterioration in lung function
Chest XRay	As indicated by respiratory status	

Routine CT chest is not recommended due to the increased lifetime risk of cancer, particularly in children.[3, 4] The argument for performing baseline high resolution CT is that bronchiectasis has been identified in patients with high resolution CT (HRCT) that was not appreciated on CXR or clinical presentation. It is also useful for comparison if a subsequent scan is performed for clinical reasons.

Some centres perform regular CT chest to monitor for the silent progression of pulmonary lesions that may occur despite appropriate therapy.[5] The general consensus of this expert group is that such investigation should not be performed as a 'routine' but would be performed as dictated by clinical status. Nevertheless, clinicians caring for patients must be vigilant to the possibility of progressive lung disease which may be subclinical.

Table 2.
Other tests that may be considered when monitoring patients on IRT

Test	**Interval**	**Potential Complication Being Assessed**
High resolution CT Chest	Baseline in Adults then as indicated by respiratory status Contraindicated in Ataxia Telangiectasia	Bronchiectasis Granuloma Lymphoid interstitial pneumonia
Serum for storage	Yearly	For later testing of virus if necessary. The risk of blood born viral infection is very low with no new cases reported since 1994
Ferritin	Six-monthly	For early detection of iron deficiency
CRP	Three-monthly	Has been advocated however the clinical significance of an elevated result remains uncertain. May be elevated in bronchiectasis/LIP

Other Supportive Care

Ongoing patient and family education regarding the underlying immune deficiency condition, potential complications of both the disease and medical interventions, as well as the importance of continued adherence with prescribed therapies is essential.

Involvement of other subspecialists (for example Respiratory Physician) and allied health professionals (for example physiotherapist or dieticians) may be warranted in the presence of organ specific co-morbidities. Genetic counselling for inherited conditions should be provided to patients and their family members where appropriate. Involvement of social worker support to ensure patients are able to access all appropriate support services to which they are entitled should be pursued. Ongoing communication with schools/work places regarding the patient's condition and the need for additional education/work place support when required is also important.

As children approach adolescence, preparation for transition to adult medical services is recommended. This involves participation in combined clinics involving the parent and adult immunology services.

Linking of families with appropriate patient support groups (for example Immune Deficiency Foundation Asia Pacific Alliance (IDFAPA)) is recommended for patient advocacy and support as well as education on new developments (Table 3). The clinical immunology service responsible for the care of the patient should ensure that newly identified patients with primary immune deficiency are entered into relevant registries, for example the Australasian Society of Clinical Immunology and Allergy (ASCIA) Register of Primary Immune Deficiency Disorders (www.immunodeficiency.org.au).

Management Of Infections During IRT

Intravenous immunoglobulin replacement therapy only replaces IgG, and does not correct defects in secretory IgA antibody. Furthermore IVIg does not provide high levels of specific antibody against all organisms. Therefore, patients on IRT are still susceptible to infections particularly sinopulmonary infections.

The main infectious complications in patients requiring IRT involve the sinopulmonary tract. Early identification of infection by clinical history (presence of purulent sputum, nasal drainage, or moist cough), or investigation (sputum culture, imaging studies), and aggressive treatment of intercurrent infections with antibiotics are essential.

Continuous prophylactic antibiotic therapy may be indicated in patients with antibody deficiency on IRT

Table 3:
Primary Immunodeficiency Resources

Organization	Website
Immune Deficiency Foundation Asia Pacific Alliance (IDFAPA) - IDF Asia - IDF Australia - IDF New Zealand - IDF Pacific	www.idfapa.org
ASCIA Register of Primary Immune Deficiency Disorders (Australia)	www.immunodeficiency.org.au
National Primary Immunodeficiency Resource Center	www.info4pi.org
Immunodeficiency Foundation (USA)	http://www.primaryimmune.org/idf.htm
Primary Immunodeficiency Association (UK)	www.pia.org.uk
European Society for Immunodeficiencies	http://www.esid.org/home.php

when recurrent infections occur despite optimal IRT. Suggested antibiotic regimens include Amoxycillin 15g/kg bd (500mg bd for adults); Amoxycillin/clavulanic acid (15/mg/kg of amoxycillin bd); trimethoprim/sulphamethoxazole 3-5mg/kg trimethoprim daily (80-160 mg trimethoprim in adults); azithromycin 10mg/kg 3 days per fortnight (500mg for adults). Antibiotics can be cycled empirically every 1-2 months in an attempt to avoid resistance.

Management Of Suppurative Lung Disease

It is recommended that patients with chronic lung disease are managed in conjunction with a Respiratory Physician:

- continuous broad spectrum antibiotic therapy may be considered (see above)
- regular chest physiotherapy for patients with chronic suppurative lung disease is important
- intensive inpatient therapy with intravenous antibiotic therapy and regular supervised physiotherapy should be considered for those with infective exacerbations lung disease

Vaccination

Influenza vaccination

The value of influenza vaccination in antibody deficient patients remains unproven and is not recommended as a routine. However, influenza vaccine may be useful in some patients with antibody deficiency as there may be induction of T cell immunity [6, 7]. IVIg is unlikely to provide coverage for new influenza strains, so immunisation with inactivated influenza vaccine may be considered in patients with underlying lung disease or other indication for influenza vaccine if there is some residual capacity for antibody production. Immunisation with influenza vaccination is recommended for immediate family members and other household residents of immunodeficient patients.

Other vaccines

In general, immunisation is not indicated in antibody deficient patients as they are unable to adequately respond to routine immunisation.

Planning cessation of IRT

In many circumstances such as X-linked agammaglobulinaemia or CVIDs, IRT is planned indefinitely.

In situations where the defect of humoral immunity is less pronounced, IRT may be initiated on a trial basis for a limited time period. It is essential to discuss the anticipated duration of IRT and expected outcomes in advance of commencement. Patients who have the expectation of indefinite therapy may be reluctant to consider cessation despite being entirely free of infections.

Assessment of humoral immunity in those continuing to receive IRT is difficult (see below) but not impossible. For this reason, both the physician and the patient may be uncertain about whether the defect of humoral immunity that triggered commencement of IRT has evolved, persisted, or even resolved in the intervening period. It is likely that a significant proportion of long term recipients of IRT, particularly those whose initial diagnosis was IgG subclass deficiency, specific antibody deficiency or where the antibody deficiency is secondary to other causes, could cease IRT without adverse effect. Ongoing use in such patients may impose an unnecessary burden on IVIg demand, medical costs and quality of life of the recipients.

Assessing residual immune function during IRT

Immunoglobulin replacement therapy, by replacing polyclonal antibody, invalidates most laboratory tests of humoral immune function. Residual production of IgG and vaccine antibody responses cannot be distinguished from antibodies in the IRT product. Several approaches have been considered in the assessment of residual immune function while on IRT. Evaluation of responses to neoantigens such as Phage vaccine-Bacteriophage øX-174 or Rabies vaccine has been used but is not currently widely available and thus of limited clinical applicability.[8]

In many circumstances such as X-linked agammaglobulinaemia or CVIDs, IRT is planned indefinitely. For those patients who have evolution of their immunological features eg. loss of IgA, IgM and isoagglutinins whilst on IRT, it could be argued that a therapeutic trial of IRT is not necessary. If the ongoing need for IRT is uncertain, a trial of IRT cessation will be required.

Re-evaluation of immunity after trial cessation

For those conditions in which IRT is to be used as a therapeutic trial (eg specific antibody deficiency with normal immunoglobulins), it is imperative that the plan to cease IRT is made prior to therapy being commenced. In general such therapeutic trials would be expected to proceed for 12 months followed by cessation and a period of ongoing clinical surveillance with immunological re-evaluation. Patients are required to be off IRT for 4-6 months before re-evaluation of endogenous immunoglobulin levels and vaccine responses (see chapter 2). This suggested time frame is based upon the understanding that it requires 4 half lives to clear 94% of exogenous immunoglobulin.

Serological tests for infection in recipients of IRT

Serological tests for infectious diseases are not helpful in patients receiving IRT as production of specific antibody (IgG, IgA and IgM) may be impaired due to the underlying humoral immune deficiency, and immunoglobulin preparations will contain IgG to common infectious organisms. Polyclonal IgG antibody from a large number of individual donors is likely to contain a concentration of microbial and vaccine antigen-specific IgG that approximates the mean level for the donor population (with the exception of excluded disorders such as HIV, syphilis and Hepatitis C virus). Therefore over reliance on a negative or positive serology test may result in false diagnosis. PCR for viral antigens should be used to assess for infection where available and appropriate.

Serology testing for autoimmune disease in recipients of IRT

Immunoglobulin replacement products may contain auto-antibodies however these are present in very low titres. In more profound antibody deficiencies such as XLA, the patient is unable to produce auto-antibodies. A negative result does not necessarily rule out autoimmune disease.

References

1. Chapel HM, Christie JM, Peach V, Chapman RW. Five-year follow-up of patients with primary antibody deficiencies following an outbreak of acute hepatitis C. Clin Immunol 2001;99(3):320-4.

2. Quinti I, Pierdominici M, Marziali M, Giovannetti A, Donnanno S, Chapel H, et al. European surveillance of immunoglobulin safety--results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. Clin Immunol 2002;104(3):231-6.

3. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. Am J Roentgenol 2001;176(2):289-96.

4. Brenner DJ, Hall EJ. Computed tomography -an increasing source of radiation exposure. N Engl J Med 2007;357(22):2277-84.

5. Rusconi F, Panisi C, Dellepiane RM, Cardinale F, Chini L, Martire B, et al. Pulmonary and sinus diseases in primary humoral immunodeficiencies with chronic productive cough. Arch Dis Child 2003;88(12):1101-5.

6. Plebani A, Fischer MB, Meini A, Duse M, Thon V, Eibl MM. T cell activity and cytokine production in X-linked agammaglobulinemia: implications for vaccination strategies. Int Arch Allergy Immunol 1997;114(1):90-3.

7. Paroli M, Accapezzato D, Francavilla V, Insalaco A, Plebani A, Balsano F, et al. Long-lasting memory-resting and memory-effector CD4+ T cells in human X-linked agammaglobulinemia. Blood 2002;99(6):2131-7.

8. Ochs HD, Davis SD, Wedgwood RJ. Immunologic responses to bacteriophage phi-X 174 in immunodeficiency diseases. J Clin Invest 1971;150(12):2559-68.

Chapter 9

Adverse events with immunoglobulin replacement therapy

- Adverse events may be immediate or delayed
- Headache is the most common adverse event
- Adverse events are more likely to occur with the first infusion or if there is active infection
- Serious adverse events are very uncommon
- Viral inactivation steps utilised in the production of immunoglobulin have made the risk of transmission of hepatitis and other blood borne virus infections remote

Administration of IVIg is associated with the risk of adverse events which may be classified as immediate, delayed or the transmission of viral infection.[1]

Immediate adverse events

Immediate adverse events (AE) are events occurring during the infusion. The more carefully a history of adverse reactions is sought, the higher the reported incidence. There are few prospective studies of the prevalence of immediate AEs and there is wide variation in immediate AE rates reported in the literature.[2,3] A recent prospective study in children showed that immediate AEs occurred in 10% of children and 4% of infusions.[2] The majority of the reactions observed were mild [4] and severe reactions were very uncommon.[5] The most common immediate AEs were headache, pain at the infusion site and vertigo. Other symptoms may include nausea, fever, arthralgia, rash, palpitations and bronchospasm. The rate of headaches during the infusion is approximately 5%. In immunodeficient adults, Brennan et al classified reactions occurring in the first 48 hours as mild, moderate and severe (Table 1), with a 0.84% rate of mild or moderate reactions in 11,004 infusions.[5] There were no severe reactions. A large ten year prospective study of one preparation (Octagam®) in patients with PIDs found immediate AEs in 8.3% of patients and 0.5% of infusions.[6] The immediate AE rate in adults appears to be greater in those who are elderly and those who have secondary immune deficiency. Thus immediate AEs occurred in 12% of myeloma patients and 2.7% of adults with chronic lymphatic leukaemia.[7]

Previous studies have suggested that many immediate AEs, particularly headaches, are infusion rate dependant. Immediate AEs are more likely to be infusion rate dependent and may be reduced if the infusion rate is slowed. The mechanism of most of these events is unknown, but many have been considered to be due to IgG aggregates in the infusion which activate inflammatory pathways, for example complement, or stimulate cytokine production. Transient hypotension has been observed and may be due to IgG dimers.[8]

Immediate adverse events are more likely to occur on the first infusion, if there is an active infection,[5] or when changing IVIg preparations [9]. Some authorities recommend that in the presence of an acute bacterial infection, administration of IVIg should be delayed for 36-48 hours while the acute infectious process is controlled.[5,7] The management of AEs is outlined in the Table 1.

If immediate AEs are significant and not alleviated by the strategies outlined in Table 1, a change of IVIg product [10] or substitution with subcutaneous administration[11] should be considered, and may result in resolution.

Table 1
Classification and management of adverse reactions

Severity	**Symptoms**	**Infusion Action**	**Prevention**
Mild	Headache, flushing, muscle aches, shivering, feeling sick, itching, urticaria, anxiety, light-headedness, dizziness or irritability	Decrease infusion rate	Consider pre-medication with paracetamol and/or antihistamine orally 45 minutes before infusion
Moderate	Mild reactions becoming worse, chest pain or wheezing	Cease infusion and when reaction subsides restart at half the rate	Pre-medication with paracetamol and/or antihistamine orally 45 minutes before infusion. If ineffective, add hydrocortisone IV 30 minutes before infusion
Severe	Moderate reactions persisting or becoming worse, tightness of the throat, severe headache and shaking, severe breathlessness or wheezing, severe dizziness or fainting, sensation of pressure in the chest or collapse	Cease infusion. Administer adrenaline Oxygen	Consider use of subcutaneous therapy
Delayed reactions	Headache	None	Ibuprofen three times daily for 24-48 hours

Anaphylaxis

Very rarely, life-threatening anaphylaxis may occur. These reactions are usually allergic, mediated by an immunologic mechanism such as IgE[12], IgG[11] or immune complex-complement related. Reactions to IVIg are frequently due to IgG anti-IgA antibodies in the recipient. As all IVIg products contain varying amounts of residual IgA (see Chapter 7), the likelihood of a reaction increases the larger the dose. Infusion of IgA-depleted IVIg minimises these reactions.[13] Subcutaneous therapy has been utilised as an alternative without the recurrence of adverse reactions.[11]

Immunoglobulin G anti-IgA antibodies may be found in patients with selective total IgA deficiency and those with common variable immunodeficiency disorders (CVIDs). These two groups of patients are at increased risk of anaphylaxis reactions due to the anti-IgA antibodies. Immunoglobulin G anti-IgA antibodies are found in about 20% of individuals with total selective IgA deficiency[14] and about 10% of patients with CVIDs.[15] The antibody levels remain relatively constant with time in those who have high or medium antibody levels.

Anti-IgA antibodies are rarely, if ever, found in patients with decreased, but detectable serum IgA[14] Reactions to residual IgA in the IVIg are not a problem in subjects with more severe antibody deficiencies such as X-linked agammaglobulinaemia, due to their inability to make functional antibodies. On some occasions, anaphylactic reactions may be due to IgE anti-IgA antibodies. As all immunodeficient subjects who have been found to have IgE anti-IgA antibodies also have IgG anti-IgA antibodies, the conclusion that the anaphylactic reaction was caused by the IgE antibodies is considered to be circumstantial.[12]

Haemolysis

Clinically significant haemolysis is rare following IVIg therapy. Intravenous immunoglobulin contains anti-A and anti-B antibodies against human ABO red cell antigens.[16] Transfusion-associated haemolysis is thought to be associated with high titres of anti-A or anti-B antibodies.[13] Haemolysis may also be caused by high titres of anti-Rh-d antibodies.[17] Haemolysis has been reported more frequently in patients receiving high-dose IVIg therapy. The haemoglobin levels of patients with pre-existing haematological disorders who are receiving high-dose IVIg should be monitored. Significant haemolysis may require the suspension of treatment or switching the patient to a different IVIg batch or product.

Transfusion-associated Acute Lung Injury (TRALI)

Transfusion-associated acute lung injury (TRALI) is a very rare complication of IVIg therapy. There are two case reports of TRALI associated with the use of IVIg.[18,19] Anti-granulocyte antibodies present in the IVIg product may be responsible.[19] If the patient develops signs and symptoms of acute respiratory distress during or shortly after the infusion of IVIg, TRALI should be considered.

Interference with glucose estimations

The maltose present in some IVIg preparations, such as Intragam® P and Octagam® can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase, resulting in falsely elevated blood glucose levels. This has lead to iatrogenic hypoglycaemia in a diabetic patient, because of administration of increased insulin doses on the basis of falsely elevated capillary glucose readings.[20] Blood glucose monitors that use the glucose oxidase system do not react with maltose and are recommended for use if there is co-existing diabetes.

Delayed adverse events

Delayed AEs may be defined as events occurring after the infusion has ceased and are more common than immediate AEs.[21] A prospective study in children recorded delayed AEs in 21% of infusions and 41% of patients.[2] Delayed AEs were four to six times more frequent than immediate reactions in patients. In children, headache was the most common delayed AE, occurring in 26% of patients and was associated with significant morbidity, defined as a significant loss of academic or leisure time.[2] Tcheurekdjian et al recorded delayed AEs in 41% of infusions in patients with primary immunodeficiency.[21] A prospective study in adults found headache in 30% of treatment courses of IVIg for neurological disease.[22] Delayed headache is very common and does not usually require further investigation. It is also possible that IVIg infusions trigger migraines, and migraines have been reported to be a risk factor for headaches following IVIg infusion.[23]

Aseptic meningitis

Aseptic meningitis is an inflammatory reaction with symptoms of severe headache associated with fever, nuchal rigidity, photophobia, nausea and cerebrospinal fluid (CSF) pleocytosis with elevated protein. Aseptic meningitis is a non-infective complication and the CSF does not contain

bacteria or viruses. It has been reported following IVIg in 17% of adults[24] and in 5% of children with idiopathic thrombocytopenia purpura (ITP).[25] Aseptic meningitis appears to be more common in patients with ITP, neurological disease or a history of migraine[23] than in immunodeficient subjects. The aetiology is unclear, but it may be due to a hypersensitivity reaction to components of the IVIg preparation. Symptoms last three to five days and resolve without sequelae. Aseptic meningitis is usually associated with high doses of IVIg and rapid administration, and recurrence is common. Symptoms may be reduced by pre-medication with an analgesic or a non-steroidal anti-inflammatory and antihistamine, and by slowing the rate of administration.

Hyponatraemia

Intravenous immunoglobulin administration can cause hyperproteinaemia and low sodium following the infusion. The low sodium is usually due to "pseudohyponatraemia" which arises from an increased percentage of protein or lipid in plasma, with a normal plasma water Na (+) concentration.[26] Occasionally, true hyponatraemia can occur due to osmotic shift of water to the extracellular compartment.[27]

Thrombosis

Thrombotic events are a rare complication of IVIg treatment.[28] Deep vein thrombosis, pulmonary embolism, myocardial infarction (MI) and stroke have all been reported.[29] From October 1997 to July 2007, Health Canada received ten reports of stroke, six reports of thrombosis, four reports of MI and two reports of pulmonary embolus, all suspected of being associated with IVIg. The median age of the patients was 61, and the youngest patient was 28 years of age (Canadian Adverse Reaction Newsletter Vol.18, Issue 1, January 2008). Arterial thrombosis is four times more common than venous thrombosis.[30] The majority of patients have received high-dose therapy for an autoimmune disorder, however, there have been reports in individuals receiving standard replacement therapy for immune deficiency. Patients with vascular disease risk factors or known vascular disease were more prone to this complication.[30] Thus older age, associated arterial hypertension and hypercholesterolaemia were recognised as risk factors.[31]

The pathological basis of thromboembolic complications is not well understood. Serum viscosity, increased platelet aggregation and the presence of factor XIa in IVIg products have all been postulated as initiating factors. Immunoglobulin G can raise blood viscosity.[26] In patients with pre-existing high blood viscosity (monoclonal gammopathies, hypercholesterolaemia), hypercoagulable states and/or impaired cardiac output, this may lead to thrombosis. Patients considered at increased risk of thrombosis should be carefully monitored for signs or symptoms of intravascular events. Patients should be adequately hydrated and rapid infusion of IVIg should be avoided.[32] Baseline assessment of blood viscosity should be considered in patients at high risk for hyperviscosity.

Neutropenia

Transient neutropenia can occur 24-48 hours after IVIg.[33] The neutrophil count returns to normal by 14 days. Autoantibodies in IVIg against sialic acid containing receptors on the neutrophil surface, have been demonstrated to cause neutropenia.[34]

Acute renal failure

In 1998 the US Food and Drug Administration drew attention to the possibility of acute renal failure (ARF) associated with the use of IVIg usually in those patients with pre-existing renal compromise. Approximately 90% of the US reported cases were associated with the use of sucrose-containing products.[35] There are also reports in the literature of ARF following the use of non-sucrose containing products. Sucrose, maltose, glucose, glycine and D-sorbitol have all been used as stabilizing agents to prevent the formation of immunoglobulin aggregates. They are excreted by the kidney and may be associated with osmotic nephropathy at high doses.[36] Acute renal failure usually occurs in the week following IVIg administration and about 40% of patients will require dialysis.

The mean time to recovery of renal function, with or without dialysis, is ten days. Patients at increased risk of developing ARF include those with pre-existing renal insufficiency, diabetes mellitus or paraproteinaemia, those over 65 years of age and those who are ill with volume depletion and sepsis, or who are receiving nephrotoxic drugs. Such patients should have their renal function monitored and should be adequately hydrated prior to the initiation of IVIg therapy.

Autoimmune events

There have been uncommon reports of the development of autoimmune disease presumed to be caused by autoantibodies in the IVIg. IgG from normal donors has also been shown to contain antibody against a number of cytokines including cytokines IL-6, interferon (IFN) α and GM-CSF.[37]

Eczema

An eczematous skin reaction with a characteristic initial localization to the palms and/or soles that then extends to the rest of the body is a rare adverse effect.[38] The reaction occurs around 7- 10 days after the IVIG infusion and resolves by 1 month. The mechanism of this is unknown but seems to be batch related.

Viral infections

The principal concern has been reports of non-A, non-B hepatitis transmitted by IVIg to immunodeficient subjects. The first report of non-A non-B hepatitis was in 1983 and this has been followed by at least 247 further cases by 1995 associated with the use of Gammagard®.[39] Of these the association between the IVIg and Hepatitis C (HCV) infection[40] was considered probable or likely in 61%, possible in 26% and unlikely in 13%. A high proportion (88%) of non-A non-B hepatitis in immunodeficient subjects was associated with a positive hepatitis C PCR. All reports of infection have been with lyophilized preparations. Lyophilization may be important in stabilizing the virus. As had been predicted, HCV-infected plasma donors who had not yet seroconverted had contaminated plasma pools used for the manufacture of IVIg. Additional viral inactivation steps such as incubation at pH4, pasteurisation, nanofiltration or solvent-detergent treatment have been incorporated into the production process of IVIg.[41] It should be realized that as immunodeficient recipients cannot mount an antibody response, serological methods cannot be used for diagnosis, and the identification of causative organisms depends on PCR testing. An additional complicating factor is the possibility that subjects may develop hepatitis unrelated to therapy. Hepatitis C infected patients often demonstrated a rapid progression of HCV infection, with end-stage liver disease in about 40% of patients, 10% of patients spontaneously cleared the virus and about 30% became asymptomatic carriers.[5,42] The clinical course of hepatitis C is not necessarily more severe in immunodeficient subjects. No other viruses are known to have been transmitted by IVIg preparations.[43] It is notable that HIV transmission by IVIg has not been reported. This is despite the fact that unscreened plasma collected in the early 1980s was used in the manufacture of gammaglobulin products at a time when HIV transmission to recipients of other blood products was occurring, indicating that the virus is inactivated during the IVIg manufacturing process.

Prions

Transmissible spongiform encephalopathies (TSEs) are rare fatal brain diseases of animals and man due to prions. There is no direct evidence of transmission of any of the TSEs by fractionated plasma products including IVIg. Inactivation of prions is not possible without destruction of the biological activity of the product and therefore only the principles of partitioning and size exclusion can be applied to eliminate prions during manufacturing of immunoglobulin preparations.[44, 45] The overall reduction by partitioning processes can exceed 9 logs. The blood products industry, plasma fractionators, and regulatory authorities have taken precautionary measures to reduce the potential risk. There is currently no screening test. The collection of blood or plasma from an individual with the inherited forms of human TSE or TSE acquired iatrogenically is limited by deferral of donors on the basis of information obtained from a medical questionnaire. Most plasma collection agencies have adopted a policy of deferral of donors who had resided in the UK for six or more months between 1980 and 1996 (the time coinciding with the height of the UK BSE epidemic).

References

1. Nydegger UE, Sturzenegger M, Adverse effects of intravenous immunoglobulin therapy. Drug Saf 1999;21:171-185.

2. Singh-Grewal D, Kemp A, Wong M. A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. Arch Dis Child 2006;91:651-654.

3. Aghamohammadi A, Farhoudi A, Nikzad M, Moin M, Pourpak Z, Rezaei N, et al., Adverse reactions of prophylactic intravenous immunoglobulin infusions in Iranian patients with primary immunodeficiency. Ann Allergy Asthma Immunol 2004;92:60-64.

4. Struff WG, Klasser M, Eckert V, Dietrich RL, Safety monitoring of a polyvalent immunoglobulin preparation: documentation of 15,548 administrations. Int J Clin Pharmacol Ther 2005;43:420-428.

5. Brennan VM, Salome-Bentley NJ, Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol 2003;133:247-251.

6. Debes A, Bauer M, Kremer S, Tolerability and safety of the intravenous immunoglobulin Octagam: a 10-year prospective observational study. Pharmacoepidemiol Drug Saf 2007;16:1038-1047.

7. Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet 1994;343:1059-1063.

8. Kroez M, Kanzy EJ, Gronski P, Dickneite G. Hypotension with intravenous immunoglobulin therapy: importance of pH and dimer formation. Biologicals 2003;277-286.

9. Ameratunga R, Sinclair J, Kolbe J. Increased risk of adverse events when changing intravenous immunoglobulin preparations. Clin Exp Immunol 2004;136:111-113.

10. Limaye S, Walls RS, Riminton S. Safe and effective use of chromatographically purified intravenous immunoglobulin despite profound anti-IgA sensitization. Intern Med J 2001;31:256-257.

11. Eijkhout HW, van den Broek PJ, van der Meer JW. Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy. Neth J Med 2003;61:213-217.

12. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. N Engl J Med 1986;314:560-564.

13. Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. Drug Saf 1993;9:254-262.

14. Koskinen S, Tolo H, Hirvonen M, Koistinen J. Long-term follow-up of anti-IgA antibodies in healthy IgA-deficient adults. J Clin Immunol 1995;15:194-198.

15. Horn J, Thon V, Bartonkova D, Salzer U, Warnatz K, Schlesier M, et al. Anti-IgA antibodies in common variable immunodeficiency (CVID): diagnostic workup and therapeutic strategy. Clin Immunol 2007;122:156-162.

16. Thorpe SJ, Fox BJ, Dolman CD, Thorpe R. Anti-A and anti-B activity in batches of different intravenous immunoglobulin products determined using a direct haemagglutination method. Biologicals 2005;33:111-116.

17. Thorpe SJ, Fox BJ, Dolman CD, Lawrence J, Thorpe R. Batches of intravenous immunoglobulin associated with adverse reactions in recipients contain atypically high anti-Rh D activity. Vox Sang 2003;85:80-84.

18. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. Transfusion 2001;41:264-268.

19. Cailleux N, Levesque H, Bastit D, Cuvelier A, Muir JF, Courtois H. [A rare cause of intra-alveolar hemorrhage: a transfusion-related incident with leukoagglutination due to antigranulocyte antibodies (Trali syndrome)]. Rev Med Interne 1998;19:434-437.

20. Kannan S, Rowland CH, Hockings GI, Tauchmann PM. Intragam can interfere with blood glucose monitoring. Med J Aust 2004;180:251-252.

21. Tcheurekdjian H, Martin J, Kobayashi R, Wasserman R, Hostoffer R. Intrainfusion and postinfusion adverse events related to intravenous immunoglobulin therapy in immunodeficiency states. Allergy Asthma Proc 2006;27:532-536.

22. Stangel M, Kiefer R, Pette M, Smolka MN, Marx P, Gold R. Side effects of intravenous immunoglobulins in neurological autoimmune disorders--a prospective study. J Neurol 2003;250:818-821.

23. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. Ann Intern Med 1994;15 121:259-262.

24. Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. Haematologica 1993;78:35-40.

25. Kattamis AC, Shankar S, Cohen AR. Neurologic complications of treatment of childhood acute immune thrombocytopenic purpura with intravenously administered immunoglobulin G. J Pediatr 1997;130:281-283.

26. Steinberger BA, Ford SM, Coleman TA. Intravenous immunoglobulin therapy results in post-infusional hyperproteinemia, increased serum viscosity, and pseudohyponatremia. Am J Hematol 2003;73:97-100.

27. Nguyen MK, Rastogi A, Kurtz I. True hyponatremia secondary to intravenous immunoglobulin. Clin Exp Nephrol 2006;10:124-126.

28. Brown HC, Ballas ZK. Acute thromboembolic events associated with intravenous immunoglobulin infusion in antibody-deficient patients. J Allergy Clin Immunol 2003;112:797-799.

29. Zaidan R, Al Moallem M, Wani BA. Shameena AR, Al Tahan AR, Daif AK, et al. Thrombosis complicating high dose intravenous immunoglobulin: report of three cases and review of the literature. Eur J Neurol 2003;10:367-372.

30. Paran D, Herishanu Y, Elkayam O, Shopin L, Ben Ami R. Venous and arterial thrombosis following administration of intravenous immunoglobulins. Blood Coagul Fibrinolysis;Jul 16:313-318.

31. Marie I, Maurey G, Herve F, Hellot MF. Levesque H, Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. Br J Dermatol 2006;155:714-721.

32. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immunol 2005;29:173-184.

33. Matsuda M, Hosoda W, Sekijima Y, Hoshi K, Hashimoto T, Itoh, S et al. Neutropenia as a complication of high-dose intravenous immunoglobulin therapy in adult patients with neuroimmunologic disorders. Clin Neuropharmacol 2003;26:306-311.

34. von Gunten S, Schaub A, Vogel M, Stadler BM, Miescher S, Simon HU. Immunologic and functional evidence for anti-Siglec-9 autoantibodies in intravenous immunoglobulin preparations. Blood 2006;108:4255-4259.

35. Chapman SA, Gilkerson KL, Davin TD, Pritzker MR. Acute renal failure and intravenous immune globulin: occurs with sucrose-stabilized, but not with D-sorbitol-stabilized, formulation. Ann Pharmacother 2004;38:2059-2067.

36. Ahsan N. Intravenous immunoglobulin induced-nephropathy: a complication of IVIG therapy. J Nephrol 1998;11:157-161.

37. Svenson M, Hansen MB, Ross C, Diamant M, Rieneck K, Nielsen H, et al. Antibody to granulocyte-macrophage colony-stimulating factor is a dominant anti-cytokine activity in human IgG preparations. Blood 1998;15 91:2054-2061.

38. Vecchietti G, Kerl K, Prins C, Kaya G, Saurat JH, French LE. Severe eczematous skin reaction after high-dose intravenous immunoglobulin infusion: report of 4 cases and review of the literature. Arch Dermatol 2006;142:213-217.

39. Gomperts ED. Gammagard and reported hepatitis C virus episodes. Clin Ther 1996; 18 B:3-8.

40. Yap PL. The viral safety of intravenous immune globulin. Clin Exp Immunol 1996;104 Suppl 1:35-42.

41. Siegel J. Safety considerations in IGIV utilization. Int Immunopharmacol 2006;6:523-527.

42. Quinti I, Pierdominici M, Marziali M, Giovannetti A, Donnanno S, Chapel H, et al. European surveillance of immunoglobulin safety–results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. Clin Immunol 2002;104:231-236.

43. Dodd RY. Infectious risk of plasma donations: relationship to safety of intravenous immune globulins. Clin Exp Immunol 1996;104 1:31-34.

44. Truchot L, Arnaud T, Bloy C, Perret-Liaudet A. CJD PrPsc removal by nanofiltration process: application to a therapeutic immunoglobulin solution (Lymphoglobuline). Biologicals 2006;2006; 34:227-231.

45. Trejo SR, Hotta JA, Lebing W, Stenland C, Storms RE, Lee DC, et al. Evaluation of virus and prion reduction in a new intravenous immunoglobulin manufacturing process. Vox Sang 2003;84:176-187.

Appendix 1

1) Patient home therapy adverse reaction report form

2) Home subcutaneous immunoglobulin infusion record

3) Infection log during home immunoglobulin treatment

Patient home therapy adverse reaction report form

- If you experience a reaction to immunoglobulin infusion please complete this form within 48 hours and forward to your immunology centre.
- Follow the instructions provided by your immunologist for recognition and management of an adverse reaction.

Patient name _____

Product name _____

Batch number _____

Date of reaction _____

General health before infusion (eg presence of infection)

_____

_____

_____

Describe the reaction

_____

_____

_____

Action taken	**Infusion stopped**	**Yes / No**
	Medication given	**Yes / No**
Please list medication	_____	
	_____	

Management for subsequent infusions (Hospital use only)

_____

_____

_____

Signature:_____ **Role:**_____ **Date:**_____

Home subcutaneous immunoglobulin infusion record

Name _____ **Weight** _____ **Product Name** _____

	Date of Infusion	Infection present?	Infection since last Infusion?	Site used Abdomen/leg	Dose per site	Total dose	Rate	Batch numbers	Comments, problems or reactions
1		yes / no	yes / no						
2		yes / no	yes / no						
3		yes / no	yes / no						
4		yes / no	yes / no						
5		yes / no	yes / no						
6		yes / no	yes / no						
7		yes / no	yes / no						
8		yes / no	yes / no						

< You should have paracetamol and anti-histamine available when you infuse
< Please list any infections on the reverse of this log and follow your immunologists instructions about infusion during infection
< If you have an adverse reaction please complete an adverse reaction form and send it (with this form) to your centre today
< Please give details overleaf if you have any problem with your infusion or have recently been admitted to hospital

Please return completed form to: _____

_____

If you have any problems please call: _____

_____

Infection log during home immunoglobulin treatment

(please list details of all infections if two at once)

Name _____

Infection onset date	Infection site *	Symptom details (use key listed below *)					GP visit yes/no	Treatment (antibiotics/other)			Days off work/school	Sample taken (please list blood, sputum etc)	Results normal yes/no	Hospital admission yes /no
		1	2	3	4	5		dose	name	no.days				

* **Infection Site** (please tick (√) for relevant symptoms in boxes above)

Chest
1. Sputum y= yellow g = green
2. Increasing cough
3. Shortness of breath
4. Chest pain
5. Fever

Sinus
1. Painful/tender sinus
2. Drip in back of throat
3. Headache
4. Nasal drip y=yellow g=green
5. Fever

Urinary
1. Increased frequency of urine
2. Burning/pain on passing urine
3. Fever
4. Accidental urine loss
5. Pain in side

Stomach/bowel
1. Diarrhoea
2. Weight loss
3. Stomach pain
4. Fever

Other
1. Eyes
2. Abscess
3. Skin
4. Ears
5. Mouth ulcers/cold sores

Please return completed form to: _____

_____

If you have any problems please call: _____

_____

Membership of Scientific Committee

AUSTRALIA

Associate Professor Mimi TANG (Chair)
MBBS PhD FRACP FRCPA
Director
Department of Allergy and Immunology
Royal Children's Hospital
Flemington Road, Parkville, Vic 3052
AUSTRALIA

Professor Andrew KEMP
MBBS (Melb) PhD (ANU) FRACP
Professor of Paediatric Allergy and
Clinical Immunology
Discipline of Paediatrics and Child Health,
University of Sydney
Department of Allergy, Immunology
and Infectious Diseases
The Children's Hospital at Westmead
Hawkesbury Rd, Westmead, NSW 2145
AUSTRALIA

Associate Professor Richard LOH
MBBS FRACP FAAAAI FACAAI
Head of Immunology and Allergy
PathWest
Princess Margaret Hospital
Roberts Road, Subiaco, WA 6008
AUSTRALIA

Associate Professor Sean RIMINTON
MBChB (Dist) PhD FRACP FRCPA
Clinical Immunologist
Concord Hospital
Hospital Road, Concord, NSW 2139
AUSTRALIA

Dr Joanne SMART
BSc MBBS PhD FRACP
Paediatric Immunologist
Department of Allergy and Immunology
Royal Children's Hospital
Flemington Rd, Parkville, VIC 3052
AUSTRALIA

Dr Melanie WONG
MBBS (Hons) PhD FRACP FRCPA
Paediatric Immunologist and Director
of Immunology Laboratory
The Children's Hospital at Westmead
Hawkesbury Rd, Westmead, NSW 2145
AUSTRALIA

HONG KONG

Professor Yu Lung LAU
MD (Hon) FHKAM FHKCP FRCPCH
Associate Dean (Research Affairs)
LKS Faculty of Medicine
University of Hong Kong
HONG KONG

MALAYSIA

Dr Intan Hakimah ISMAIL
MD MMed (Paediatrics)
Paediatrician, Immunology Unit
Department of Paediatrics, Faculty of Medicine
and Health Sciences
University Putra Malaysia
43400, Serdang, Selangor
MALAYSIA

Professor Lokman Mohd. NOH
MBBS FRCP FIBCI
Cluster Immunology, Advanced Medicine
and Dental institute
University Sains, Lat 1-8, Pesiaran Seksyen 4/1
Bandar Bertam Putra, Kepala Batas 13200
Penang
MALAYSIA

NEW ZEALAND

Dr Marianne EMPSON
BHB MBChB MMed (Clin Epi) FRACP FRCPA
Clinical Immunologist
Senior Lecturer in Clinical Immunology and
Molecular Medicine and Pathology
Immunology Department, Auckland City Hospital
University of Auckland
Auckland 1
NEW ZEALAND

Dr Jan SINCLAIR
MBChB FRACP
Paediatric Allergy and Clinical Immunology
Level 5, Starship Hospital
Private Bag 92024
Auckland
NEW ZEALAND

SINGAPORE

Adjunct Professor LEE Bee Wah
MBBS MMed (Paediatrics) MD FRCP FAMS
FAAAAI
Department of Paediatrics
National University of Singapore
Mount Elizabeth Medical Centre
SINGAPORE

UNITED KINGDOM

Dr Helen CHAPEL
MA Cantab MBBChir MD Cantab FRCP FRCPath
Department of Clinical Immunology
Nuffield Department of Medicine
University of Oxford
UNITED KINGDOM

Acknowledgements

The Asia Pacific Immunoglobulins in Immunology Expert Group Inc. (APIIEG) wishes to acknowledge the following:

- The Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) and the Australasian Society of Clinical Immunology and Allergy (ASCIA) for their feedback on a draft version of the consensus recommendations and APAAACI's endorsement of the final document
- CSL Bioplasma for the unrestricted educational grant that supported the production of these consensus recommendations whilst allowing the group to remain autonomous and independent.

Terminology

Terminology

Standards Australia and virtually all national bodies around the world are following the rules set down by the International Standards Organisation (ISO) for the use of the terms 'shall', 'should' and 'may'. The *Consensus Recommendations for the Use of Immunoglobulin Replacement Therapy in Immune Deficiency* has used these definitions for consistency with current international usage:

- The term 'shall' indicates a mandatory requirement; however this does not imply a mandatory or legal requirement
- The term 'should' implies a recommendation where guidance is intended and does not preclude other acceptable practices
- The term 'may' is used to indicate an acceptable alternative or addition to the prescribed practice.

Waiver of Liability

Waiver of Liability

The information contained in this document is intended to serve as a guideline only. Neither the contributing authors nor the Asia Pacific Immunoglobulins in Immunology Expert Group shall be liable for any actions, claims, damages, costs or obligations that may arise from the inappropriate use or misuse of the material contained in this document.


APIEG
Asia Pacific Immunoglobulins In Immunology Expert Group