

# AN UPDATE OF THE PRIMARY ANTIBODY DISORDERS

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## ABSTRACT

More than 200 primary immunodeficiency diseases (PIDs) have been described and the molecular basis of more than 120 characterised. Primary antibody deficiencies are the most common group. Approximately 50% of patients with PIDs have a primary antibody deficiency, and at least 80% of all primary antibody deficiencies are due to four conditions, namely, transient hypogammaglobulinaemia of infancy, IgG subclass deficiency, partial antibody deficiency with impaired polysaccharide responsiveness and selective IgA deficiency (SIgAD). Many primary antibody deficiencies either cause arrest during early B-lymphocyte development or impede the terminal differentiation of B lymphocytes. Several gene mutations including Bruton's tyrosine kinase (Btk) deficiency,  $\mu$  heavy chain deficiency,  $\lambda 5$  deficiency, Ig $\alpha$  deficiency and Ig $\beta$  deficiency may cause arrest in early development. The molecular analysis of common variable immunodeficiency (CVID) has gained momentum. Mutations in genes encoding inducible T-cell costimulator, CD19, B-cell-activating factor receptor, transmembrane activator, calcium-modulating cyclophilin-ligand interactor, and the homolog of *Escherichia coli* MutS have been associated with CVID. Genetic research has suggested that CVID and SIgAD are related conditions. However, significant immunological differences between the two conditions exist. These observations should influence future CVID- and SIgAD-related research. The current classification of primary antibody deficiencies is discussed, and recent publications on clinical presentation and approach to diagnosis are reviewed.

## INTRODUCTION

The classic primary immunodeficiency diseases (PIDs) are relatively rare, occurring with a frequency of 1:500 to 1:500 000 in the general population.<sup>1</sup> More than 200 PIDs have been described and the molecular bases of more than 120 have been characterised.<sup>2</sup> Primary antibody deficiencies as a group represent the most common type of PIDs in humans. They are a heterogeneous group of disorders in which the defining characteristic is the inability to produce an effective antibody response to a pathogen. Most antibody deficiencies have been associated with single gene mutations causing defects in the development and function of B lymphocytes. However, some may result from environmental triggering in genetically predisposed individuals and a few are caused by delayed immunological maturation.<sup>3</sup> More than 80% of confirmed antibody defi-

ciencies that are listed in national registries are due to four antibody deficiencies, namely transient hypogammaglobulinaemia of infancy, isolated IgG subclass deficiency, partial antibody deficiency with impaired polysaccharide responsiveness and selective IgA deficiency.<sup>4</sup> This paper reviews aspects of the primary antibody deficiencies, particularly recent developments in the published literature with regard to their classification, pathogenesis, presentation and treatment.

## B-CELL DEVELOPMENT

Characterisation of the molecular events which direct the sequential development of lymphocytes has aided the elucidation of the pathogenesis of many primary antibody deficiencies. Studies of naturally occurring mutations and molecularly engineered mouse models have benefited this work.<sup>5</sup> Haemopoietic stem cells pass through several developmental stages before mature B lymphocytes are produced. Development primarily occurs in the bone marrow compartment. Mutations in genes encoding proteins that are critical for the development of the B-lymphocyte lineage, particularly between the pro-B-cell and immature B-cell stages, may disrupt B-lymphocyte maturation leading to partial or complete developmental arrest with decreased B-lymphocyte number and profoundly reduced immunoglobulin isotype (IgA, IgM, IgG, IgD, IgE) concentrations. By contrast, mutations in key genes encoding proteins that regulate terminal differentiation and function of mature B lymphocytes may result in reduced immunoglobulin isotype concentrations usually without a change in B-lymphocyte number (Fig. 1).<sup>2,5,6</sup>

## PRIMARY ANTIBODY DISORDERS

The International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee recently published an updated classification of all known PIDs. The classification of the primary antibody deficiencies has undergone several revisions since 1990 as a result of the molecular advances. Six categories have been defined (Table I).<sup>7</sup>

### *Btk* deficiency and related conditions

One of the significant advances in recent times was the elucidation of deficiencies associated with the arrest of early B-lymphocyte development. Bruton's tyrosine kinase (Btk) deficiency or X-linked agammaglobulinaemia, an X-linked recessive condition, was the first antibody deficiency to be recognised in 1952.<sup>8</sup> The molecular defect in Btk deficiency was described in 1993.<sup>9</sup> Although Btk is expressed during all stages of B-lymphocyte development except for plasma cells, deficiency causes arrest at the pre-B-cell stage. This may be detected on bone marrow analysis (Fig. 1). Btk deficiency is fully penetrant, only males are affected and the condition exhibits considerable clinical heterogeneity. However, the majority of patients are diagnosed before the age of 5 years.<sup>10</sup> Recently, the mutation of a large family with Btk deficiency in Cape Town was characterised.<sup>11</sup> About 85% of patients with early-onset infections, profound hypogammaglobulinaemia and markedly reduced B-lymphocyte number, have Btk

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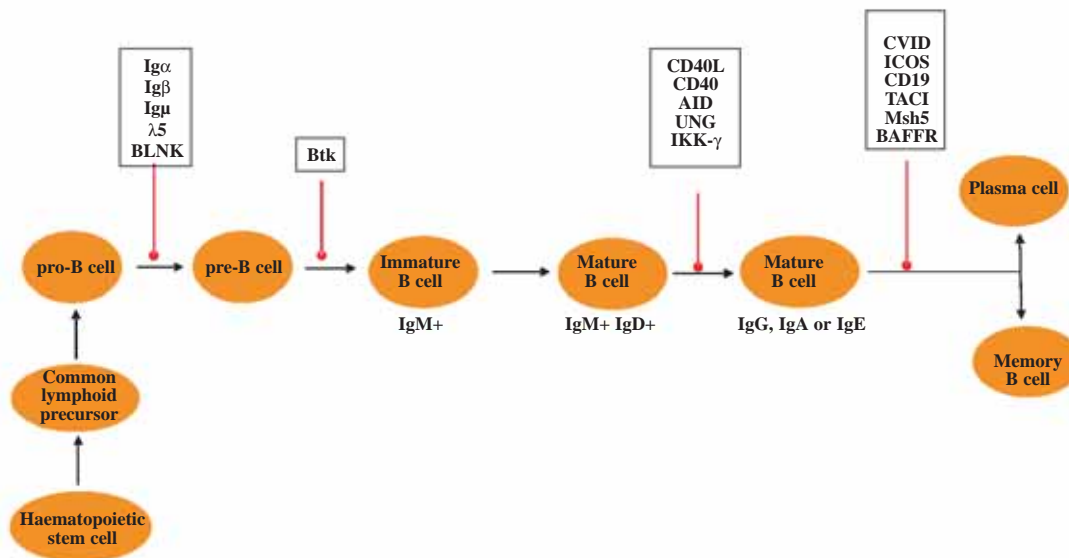


Fig. 1. B-lymphocyte development and associated primary antibody deficiencies. *Igα*, *Igβ*, *μ* heavy chain (*Igμ*), *λ5*, B-cell linker protein (BLNK) and Bruton's tyrosine kinase (*Btk*) deficiencies affect early B-lymphocyte development. Deficiencies affecting terminal B-lymphocyte function include inhibitor-of-nuclear-factor- $\kappa$ B kinase (*IKK-γ*), conditions causing hyper-IgM syndrome (*CD40* and *CD40* ligand (*CD40L*)), activation-induced cytidine deaminase (*AID*) and uracil-DNA glycosylase (*UNG*) deficiencies), and disorders associated with common variable immunodeficiency (CVID) including inducible costimulator (*ICOS*), *CD19*, transmembrane activator and calcium-modulating cyclophilin-ligand interactor (*TACI*), homolog of *Escherichia coli MutS* (*Msh5*), and possibly B-cell-activating-factor receptor (*BAFFR*).

deficiency. Deficiencies of several components of the pre-B-cell receptor complex may also cause this phenotype, including mutations in the genes encoding  $\mu$  heavy chain,  $\lambda 5$  and *Igα* and *Igβ*. In addition, mutations in the gene encoding the scaffold protein, B-cell linker protein (BLNK); may produce a similar phenotype.

Unlike *Btk* deficiency all of these deficiencies are transmitted by autosomal recessive inheritance.<sup>12-15</sup>

### Hyper-IgM syndromes

During a primary infection, antigen binds to B lymphocytes, displaying cell-surface-bound IgM. Thereafter, B

Table I. Current classification of primary antibody deficiencies

I.	Severe reduction in all serum immunoglobulin isotypes with profoundly reduced or absent B lymphocytes. Bruton's tyrosine kinase ( <i>Btk</i> ) deficiency $\mu$ heavy chain deficiency $\lambda 5$ deficiency <i>Igα</i> deficiency <i>Igβ</i> deficiency B-cell linker protein (BLNK) deficiency Thymoma with immunodeficiency Myelodysplasia
II.	Severe reduction in serum IgG and IgA with normal, low or very low numbers of B cells Common variable immunodeficiency disorders (Mutations in transmembrane activator and calcium-modulating cyclophilin – ligand interactor ( <i>TACI</i> ), B-cell-activating-factor receptor ( <i>BAFFR</i> ) and <i>Msh5</i> may act as contributing polymorphisms) Inducible costimulator ( <i>ICOS</i> ) deficiency <i>CD19</i> deficiency X-linked lymphoproliferative syndrome
III.	Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells <i>CD40</i> ligand deficiency <i>CD40</i> deficiency Activation-induced cytidine deaminase deficiency Uracil-DNA glycosylase ( <i>UNG</i> ) deficiency
IV.	Isotype or light chain deficiencies with normal numbers of B cells <i>Ig</i> heavy chain deletions $\kappa$ chain deficiency Isolated IgG subclass deficiency IgA deficiency associated with IgG subclass deficiency Selective IgA deficiency
V.	Specific antibody deficiency with normal immunoglobulin concentrations and normal numbers of B cells
VI.	Transient hypogammaglobulinaemia of infancy with normal numbers of B cells

lymphocytes refine the primary antibody repertoire generating a highly specific antibody response. Two mechanisms, class switching and somatic hypermutation are involved in antibody refinement. These mechanisms are T-lymphocyte dependent and take place in the germinal centres of secondary lymphoid organs.<sup>16</sup> Hyper-IgM (HIGM) syndromes are a group of conditions characterised by impaired immunoglobulin class switching and somatic hypermutation. Patients with these syndromes have an increased susceptibility to bacterial infection, normal numbers of peripheral B lymphocytes but low memory B lymphocytes (CD27+ B lymphocytes), normal or increased IgM, and low or absent levels of IgA, IgG and IgE. In addition, there is increased susceptibility to *Pneumocystis jirovecii* pneumonia, and chronic diarrhoea and ascending cholangitis caused by *Cryptosporidium*.<sup>17</sup>

The X-linked form of HIGM was characterised in 1993. It is due to mutations in the CD40 ligand (CD40L) gene. CD40L is expressed on T lymphocytes, and signalling via CD40 triggers terminal B lymphocyte differentiation by class switching and somatic hypermutation. CD40L deficiency is responsible for approximately two-thirds of cases of HIGM.<sup>16</sup> In 2003 the first South African kindred with X-linked HIGM was fully characterised.<sup>18</sup> Autosomal recessive forms of the HIGM, CD40L deficiency, activation-induced cytidine deaminase (AID) deficiency and uracil-DNA glycosylase (UNG) deficiency have been described. Another form of HIGM associated with anhydrotic ectodermal dysplasia is caused by mutations in the gene that encodes inhibitor-of-nuclear-factor- $\kappa$ B kinase- $\gamma$  (IKK- $\gamma$ ).<sup>19</sup> Approximately 25% of patients with the HIGM phenotype have normal expression of CD40L, CD40, AID and UNG. Research towards defining the molecular basis of this group of patients is ongoing.<sup>16</sup>

### Common variable immunodeficiency

Common variable immunodeficiency (CVID) is a heterogeneous group of diseases associated with

hypogammaglobulinaemia. In most cases inheritance is sporadic. Males and females are equally affected. The peak incidence occurs during the second and third decades of life.<sup>20</sup> T-lymphocyte proliferation following mitogen stimulation is impaired in 40% of patients with CVID and is directly associated with serum levels of IgG.<sup>21</sup> Criteria for diagnosing CVID have been published by the European Society for Immunodeficiencies (ESID) (Table II).<sup>22</sup> During the last 10 years several gene defects have been identified in patients with the CVID phenotype. Mutations in the Btk gene, and the X-linked lymphoproliferative disease gene, SH2DIA may infrequently be associated with the CVID phenotype.<sup>23-24</sup> More recently CVID has been associated with four additional monogenic defects: inducible T-cell costimulator (ICOS), CD19, transmembrane activator and calcium-modulating cyclophilin-ligand interactor (TACI), and the homolog of *Escherichia coli* MutS (Msh5), a mismatch repair protein. All four proteins are involved with terminal B-lymphocyte differentiation, including the regulation of class-switching and B-lymphocyte memory generation.<sup>25-29</sup> A search for mutations in the gene encoding B-cell-activating-factor receptor (BAFFR) yielded a defect in one adult patient with hypogammaglobulinaemia.<sup>30</sup> These recent findings suggest that the elucidation of the molecular events underpinning terminal B-lymphocyte differentiation may help to clarify CVID.

### Selective IgA deficiency

Selective IgA deficiency (SIgAD) is the most common PID, with a prevalence of 1:400 to 1:3 000 in healthy blood donors.<sup>21</sup> The condition is asymptomatic in most individuals. However, there is an association with recurrent, mainly sinopulmonary infection, gastrointestinal diseases, atopy, autoimmune disease and other diseases. Patients with severe infections are likely to have an associated IgG subclass deficiency.<sup>31</sup> The ESID criteria for diagnosing SIgAD are listed in Table II.<sup>22</sup> The condition is probably caused by defective dif-

Table II. Diagnostic criteria for common variable immunodeficiency (CVID) and selective IgA deficiency (SIgAD)

#### I. CVID

##### Probable

Male or female patient with marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria:

1. Onset of immunodeficiency at greater than 2 years of age
2. Absent isohaemagglutinins and/or poor response to vaccines
3. Defined causes of hypogammaglobulinaemia have been excluded

##### Possible

Male or female patient with marked decrease (at least 2 SD below the mean for age) in at least one of the major isotypes (IgM, IgG and IgA) and fulfills all of the following criteria:

1. Onset of immunodeficiency at greater than 2 years of age
2. Absent isohaemagglutinins and/or poor response to vaccines
3. Defined causes of hypogammaglobulinaemia have been excluded

#### II. SIgAD

##### IgA deficiency

##### Definitive

Male or female patient older than 4 years of age who has a serum IgA < 0.07 g/l but normal serum IgG and IgM, in whom other causes of hypogammaglobulinaemia have been excluded. These patients have a normal IgG antibody response to vaccination.

##### Probable

Male or female patient older than 4 years of age who has a serum IgA at least 2 SD below normal for age but normal serum IgG and IgM, in whom other causes of hypogammaglobulinaemia have been excluded. These patients have a normal IgG antibody response to vaccination.

ferentiation of B lymphocytes to IgA-secreting plasma cells, as a result of disablement of isotype class switching. Familial studies suggest an allelic relationship between SIgAD and CVID.<sup>32</sup> Mutations in the genes encoding TACI and Msh5 have been identified in patients with SIgAD, further supporting the link between SIgAD and CVID.<sup>28,29</sup> However, T- and B-lymphocyte subpopulations and activation/differentiation markers differ significantly between the two conditions. With the exception of abnormalities in the numbers of CD4+ and CD8+ lymphocytes, no major abnormalities were observed in patients with SIgAD.<sup>33</sup> Despite the genetic overlap, these immunological differences require molecular elucidation.

### *Transient hypogammaglobulinaemia of infancy*

During intrauterine life maternal IgG is actively transferred to the fetus. At birth, the IgG concentration of term infants is equal to or greater than maternal IgG concentration. Because most IgG is transferred during the second half of intrauterine life, preterm infants have a lower IgG concentration at birth. Maternal IgG in the infant disappears after birth with a half-life of 25-30 days, and intrinsic IgG production usually begins immediately after birth.<sup>34</sup> In transient hypogammaglobulinaemia of infancy, intrinsic immunoglobulin production is delayed for up to 36 months, resulting in low IgG and IgA concentrations, but IgM concentration may be normal or low. Consequently, the physiological IgG nadir between 3 and 6 months of life is exaggerated and prolonged.<sup>35-37</sup> Delayed production results in increased susceptibility to sinopulmonary infections. It is usually a self-limiting disease. In the majority of patients immunoglobulin concentrations normalise between 2 and 4 years of age.<sup>36,37</sup> Long-term follow-up and re-evaluation of immunoglobulin responses are required to exclude other primary antibody disorders.<sup>35</sup>

### *Isolated IgG subclass deficiency*

This condition is characterised by decreased concentration of one or more IgG subclass. The laboratory methods for determining IgG subclass concentrations have not been adequately standardised and age-related population norms are not always available, creating diagnostic uncertainty. Low levels of IgG2 are frequent in children, particularly in association with poor responses to polysaccharide antigens. IgG4 levels vary widely and many completely healthy people have no demonstrable IgG4 on standard testing. Therefore isolated IgG4 is difficult to interpret. Isolated IgG subclass deficiency is usually asymptomatic but may be associated with recurrent viral/bacterial infections, frequently involving the respiratory tract.<sup>7,34,35</sup>

### *Specific antibody deficiency with normal immunoglobulin concentration*

Failure to respond to polysaccharide antigens, an IgG2 subclass response, is a feature of specific antibody deficiency. This results in recurrent or persistent sinopulmonary infections. Immunisation with conjugate polysaccharide vaccines induces IgG1 and IgG3 subclass responses thereby providing immunological protection against recurrent infections.<sup>7,34,35</sup>

## **CLINICAL MANIFESTATIONS**

Failure to recognise PIDs early and to implement appropriate treatment can lead to serious morbidity and early mortality. Because of the rarity of these conditions, awareness outside immunology circles is low, often resulting in a delay in diagnosis. A review of 93

children diagnosed with PIDs at Red Cross Children's Hospital over a 14-year period showed that only 16% were diagnosed during the first year of life, 44% presented between 1 and 5 years of age, 37% between 5 and 16 years and 3% were more than 16 years old at the time of diagnosis.<sup>38</sup> Primary antibody deficiencies begin to manifest with recurrent bacterial infection from 4-6 months of age, in parallel with the physiological decline in maternally acquired IgG. Delayed recognition leads to infective and non-infective complications.<sup>3</sup>

History is the most important aspect of clinical evaluation. Patients at any age with recurrent infection, especially involving the upper and lower respiratory tracts, where the frequency and/or severity is atypical should be considered for investigation for a primary antibody deficiency. Children may in addition present with fever of unknown origin, failure to thrive and poor school attendance, related to recurrent infections. In South Africa, socioeconomic factors such as overcrowding, malnutrition, aeropollutants including cigarette smoke and exposure to open fires, and HIV infection are more frequently associated with recurrent infection.<sup>39</sup> A recent systematic review provided clear insights into the clinical manifestations and complications of the primary antibody deficiencies. Recurrent respiratory and sinus infection occurred in as many as 90% and 98% of patients respectively in published cohorts (Table III). Primary antibody deficiencies are commonly associated with bacterial infection. However, infection due to enteroviruses, *Cryptosporidium* and *Giardia* species may occur (Table IV).<sup>3,35,40</sup>

Patients may present with clinical manifestations other than recurrent infection. Many patients with CVID develop autoimmune problems. Abnormal lymphoid tissue including nodular lymphoid hyperplasia of the gut wall or congenital absence of tonsils, hepatosplenomegaly, isolated splenomegaly, atrophy, atopic eczema, haematological complications or organ-specific autoimmune diseases may be the initial presentation.<sup>3,40</sup> Autoimmunity often results from the inability of the host to eradicate microbial pathogens. The resultant chronic inflammatory response damages the surrounding tissue. Thus autoimmunity is not associated with a breakdown of self-tolerance. Instead, tissue damage occurs as the host tries to clear foreign immunogens. Autoimmunity is associated with CVID, isolated IgA deficiency and HIGM syndromes. T-lymphocyte dysregulation may contribute to the observed autoimmunity.<sup>41</sup>

The clinical presentation of conditions causing HIGM syndrome is dependent on the underlying genetic abnormality. Patients with CD40L deficiency, usually manifest with severe bacterial infections during infancy. Respiratory infections are common and up to 40% of patients develop *P. jirovecii* pneumonia. Diarrhoea occurs in more than 50% of patients and the majority follow a chronic course. *Cryptosporidium* causes chronic diarrhoea and ascending cholangitis. A wide

*Table III. Presenting infections in patients with primary antibody deficiencies*

Respiratory/chest infections	37-90%
Recurrent sinus infections	19-98%
Gastrointestinal infections	6-38%
Cutaneous infections	1-13%
CNS/meningitis	2-9%
Septic arthritis/osteomyelitis	1-7%
Ophthalmic infections	1.4-10%

range of haematological problems occur. Neutropenia is present in two-thirds of patients. Patients with CD40L deficiency commonly develop autoimmune manifestations including neutropenia, thrombocytopenia, seronegative arthritis and inflammatory bowel disease.<sup>16,17,35</sup> Patients with CD40 deficiency tend to have a pattern of severe recurrent infection and failure to thrive. However, *P. jiroveci* infection is unusual and autoimmune haematological complications do not occur. A characteristic feature is lymphoid hyperplasia with lymphadenopathy. In contrast to the lymph nodes in CD40L deficiency that lack germinal centres, in CD40 deficiency lymph nodes have large germinal centres.<sup>16,42</sup> Patients with AID deficiency or UNG deficiency have a milder clinical presentation of recurrent infection, lack opportunistic infection and their diagnosis may occasionally go unrecognised until the second or third decade of life.<sup>16</sup>

X-linked lymphoproliferative syndrome (XLP) has been classified as a primary antibody deficiency. It is caused by mutations in the SH2DIA gene which encodes the protein, SLAM-associated protein (SAP). This protein regulates signal transduction of the SLAM-family receptors and therefore contributes to crosstalk between B- and T-lymphocytes. The main clinical phenotypes in patients with XLP include fatal infectious mononucleosis due to Epstein-Barr virus (EBV) in 50% of cases, and in surviving patients recurrent infections due to hypogammaglobulinaemia (30%) and lymphoma (25%).<sup>43,44</sup>

## INVESTIGATIONS

A detailed clinical evaluation should direct the laboratory investigation of recurrent infection. Several patterns of infection occur which clinicians should learn to recognise.<sup>1</sup> Primary antibody conditions commonly manifest with recurrent upper and lower respiratory tract infection, due mainly to a spectrum of extra-cellular bacteria (Table IV). Special features include unexplained bronchiectasis, autoimmune phenomena (CVID, SIgAD, X-linked HIGM), enteroviral meningoencephalitis (Btk deficiency), *P. jiroveci* pneumonia (X-linked HIGM), Epstein Barr virus infection (XLP) and gastrointestinal disorders (CVID). The differential diagnosis includes other causes of recurrent infections such as socioeconomic factors, HIV infection, gastrooesophageal reflux, allergies and cystic fibrosis.<sup>1,34,39</sup>

If primary antibody deficiency is suspected then screening investigations should include full blood count and differential count, peripheral smear for granulocyte

morphology, platelet volume, IgA, IgG, IgM and a complement screen (CH50). In addition, granulocyte disorders and combined immune deficiency may be excluded with additional tests, nitro-blue tetrazolium test and lymphocyte subset quantification (CD3+ [total] lymphocytes, CD4+ [helper] cells, CD8+ [suppressor] cells, CD19+ or CD20+ [B] lymphocytes and CD16+ and/or CD56+ [natural killer] cells). From these investigations it may be established if an antibody deficiency is present and the major deficiency type (Table V). Immunoglobulin concentrations in children should be compared against age-related norms.<sup>1,34</sup>

Normal immunoglobulin levels do not exclude a specific antibody deficiency. Specific antibody production should be investigated. Isohaemagglutinins are naturally occurring IgM antibodies to the ABO blood group substances. By 1 year of age, 70% of infants have positive isohaemagglutinin titres. Isohaemagglutinin titres may be measured at local blood banks. Titres  $\geq 1$  in 8 to A<sub>1</sub> and B cells are usually present in normal individuals. Responses to protein antigens fall within the IgG1 subclass. Titres to protein antigens, e.g. tetanus toxoid, may be determined in vaccinated children. The response to polysaccharide vaccines, e.g. 23-valent pneumococcal polysaccharide vaccine, reside within the IgG2 subclass. Conjugate polysaccharide vaccines are not helpful in the functional evaluation of an IgG2 subclass deficiency or a selective polysaccharide antibody deficiency because the responses to conjugate vaccines fall within the IgG1 and IgG3 subclasses.<sup>34,35,39</sup> Advanced immunological testing requires specialised assays such as the detection of CD40L expression by flow cytometry in patients with an immunoglobulin pattern consistent with HIGM syndrome and assays to screen for and characterise genetic mutations. Few specialised investigations are currently available in South Africa.

## TREATMENT

For many primary antibody deficiencies intravenous immunoglobulin G (IVIG) replacement therapy is the treatment of choice. The intravenous route is preferred because it avoids painful intramuscular injections. Generally 300-600 mg per kg every 3-4 weeks is recommended. Life-long replacement is indicated for severe, genetically confirmed disorders including Btk deficiency, related conditions and CVID. In CVID without a molecular genetic diagnosis, IVIG should initially be administered for a period of 1-5 years followed by

Table IV. Micro-organisms causing common infections

Infection	Common organisms
Sinopulmonary	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Moroxella catarrhalis</i> <i>Staphylococcus aureus</i>
Septic arthritis	<i>Mycoplasma</i> spp. <i>Staphylococcus aureus</i>
Genitourinary	<i>Ureaplasma</i> spp.
Meningitis	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i>
Gastrointestinal	<i>Cryptosporidium</i> spp. <i>Giardia</i> spp.
Meningoencephalitis (Btk deficiency)	Enteroviruses

Table V. Major types of primary antibody deficiencies

Disease	B cells	Immunoglobulins
Btk deficiency	Absent/low	Low IgG, IgA, IgM
CVID	> 1%	Low IgG, IgA Normal/low IgM
HIGM syndromes	Normal	Raised IgM Low IgG, IgA
Isolated IgG subclass deficiency	Normal	Normal
Selective IgA deficiency	Normal	Low IgA Normal IgG, IgM
Specific antibody deficiency	Normal	Normal

CVID - common variable immunodeficiency, HIGM syndromes - hyper-IgM syndromes.

re-evaluation of serum immunoglobulin concentrations since hypogammaglobulinaemia may be transient and resolve spontaneously.<sup>45,46</sup>

IVIg is not indicated in IgA deficiency. In patients with IgA deficiency, transient hypogammaglobulinaemia of infancy or isolated IgG subclass deficiency plus recurrent infections, prophylactic antibiotics may be administered, using amoxicillin (twice daily) or azithromycin (weekly). In transient hypogammaglobulinaemia of infancy IVIg replacement may be used in children with severe, recurrent infections until immunoglobulin production normalises. Patients with isolated IgG subclass deficiencies account for the greatest misuse of IVIg. Immunoglobulin therapy should be used for a minority of patients who are unable to produce specific antibody and continue to experience recurrent infections despite prophylactic antibiotics.<sup>35,39,40</sup>

The treatment of HIGM syndromes includes the administration of IVIg. In patients with X-linked HIGM, IVIg does not prevent the development of sclerosing cholangitis and malignancy.<sup>17</sup> Alternative therapies have been employed successfully including granulocyte-colony-stimulating factor for neutropenia, allogeneic bone marrow transplantation (BMT) or cord blood cell transplantation to cure X-linked HIGM, and combined BMT and liver transplantation to address X-linked HIGM complicated by end-stage liver failure.<sup>17,47-50</sup> Similarly, X-linked lymphoproliferative syndrome has been treated with IVIg and BMT.<sup>43</sup>

## OUTCOME

Inadequate diagnosis or suboptimal treatment places the patient at risk of recurrent infections, organ-specific complications and early mortality. Recurrent respiratory infections may lead to bronchiectasis and end-stage lung disease with cor pulmonale and respiratory failure. Abnormal lung functions, usually an obstructive pattern, have been reported to be more common in CVID than in Btk deficiency. Lung functions should be monitored regularly to ensure that IVIg replacement is optimised to prevent these complications.<sup>3,40</sup>

Gastrointestinal disorders occur in 20-47% of patients with primary antibody deficiencies.<sup>3</sup> Hepatic complications may occur as a result of specific viral infections such as hepatitis C and primary biliary cirrhosis, often associated with *Cryptosporidium parvum* infection. In X-linked HIGM this invariably leads to end-stage liver failure.<sup>50</sup> Primary antibody deficiencies are associated with an increased risk for malignancy, varying from 1.8- to 13-fold. Lymphoreticular malignancies, particularly non-Hodgkin's lymphomas are most frequent. Other complications include disability arising from meningitis, neurodegeneration and autoimmune phenomena.<sup>3,40</sup> Despite these problems many well-managed patients respond to appropriate treatment resulting in improved life expectancy and decreased infectious complications.

In conclusion, many primary antibody deficiencies have been comprehensively characterised. The increased knowledge has impacted favourably on treatment and long-term prognosis.

## Declaration of conflict of interest

The author declares no conflict of interest.

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