SECTION 2
Indications for immunoglobulin replacement therapy in primary immune deficiency

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The prevention of infections and normalising selective immunoglobulin (sIg) levels to achieve individualised treatment, has remained the cornerstone of Ig replacement therapy (IRT) for antibody related immune deficiencies. The replacement therapy is with IgG, hence the antibody referred to is IgG.

The majority of currently described primary immune deficiencies (PIDs) are antibody-related, and the continued discovery of new PID diagnoses makes individual IRT guidelines for each specific diagnosis impractical. Where possible, however, an individual patient plan should be followed, as the requirements both medical and social differ widely amongst patients and different settings. Currently in South Africa, availability of plasma and IRT choice is restricted by limited donor pool, high cost and intermittent lack of availability and restricted range of products.

IRT is lifesaving and essential therapy for patients with immune deficiency states. It is indicated for the majority of antibody and combined immune deficiencies characterised by a lack of/and or impaired antibody function. In severe, and genetically confirmed antibody deficiency states, the replacement is lifelong, and no alternative therapy exists for these conditions.

IRT may also need to be initiated before the definitive diagnosis of a PID can be established to prevent morbidity such as organ damage. The response to therapy, ultimate diagnosis, and the potential for curative treatment (e.g., haematopoietic stem-cell transplantation) will determine the length of therapy.

A modified broad antibody PID phenotype grouping approach of the Working Group of the American Academy of Allergy, Asthma and Immunology is used for the purpose of this guideline. They are divided into three groups according to:

1. Presence of B cells (antibody producing cells).
2. Quantity of IgG antibody (antibody production failure).
3. Quality of IgG antibody (antibody function failure).[1]

Table 1: Phenotype grouping approach to identify patients that may benefit from IRT (adapted from Stiehm, *et al*)[5]

Category	B cells	IgG quantity	IgG quality (antigen-specific antibody)	Diagnostic examples
I*	Absent	Absent	Absent	• Agammaglobulinaemia • Severe combined immune deficiency (SCID)
II	Present	Low	Low	• Hyper IgM • Common variable immune deficiency (CVID) • Nuclear factor-kappa B Essential Modulator deficiency (NEMO) (subset)
III	Present	Normal	Low	• Specific antibody deficiency • NEMO deficiency (subset) • Subclass deficiency with specific antibody defect
IV**	Present	Low	Normal	• Transient hypogammaglobulinaemia of infancy • Primary hypogammaglobulinaemia

Notes: *A subgroup of SCID patients have B-cells present and will require IRT. B+ SCID patients must be included under category I.
**Documentation of specific antibody function should be performed in these individuals and if impaired should prompt their being considered for a category II diagnosis.

High quality evidence, GRADE A (level A or established evidence-based randomised controlled trials) according to the Grading of Recommendations Assessment, Development and Evaluation to rate quality of evidence in accordance with Cochrane reviews [2], supports the therapeutic use of IRT in primary antibody deficiency states for PID with lack of B cells and or low IgG antibody levels. [1,3]

Good practice point (current consensus opinion in the absence of level A evidence) supports the use of IRT in specific antibody deficiency.[4] Transient hypogammaglobulinaemia of Infancy (THI), which can mature up to four years of age and IgA deficiency do not warrant IgG replacement therapy unless accompanied by persistent, recurrent, or invasive infection, in which case a subclass deficiency or other immune defect should be investigated.

While the aim of IRT is prevention of all infections, mucosal immunity, specifically IgA, is not restored by IgG replacement and patients with antibody defects may still experience symptoms such as diarrhoea, and those with established bronchiectasis or other end organ damage, may still experience infections and require prophylactic antibiotics in addition.

Antigen-specific IgG levels, or the so-called vaccine responses, can be variable in patients with a dysfunctional humoral immune system and should be followed longitudinally. A normal level on one occasion does not exclude an immunodeficiency and should be evaluated at a later stage for waning antibody levels. Antibodies must be measured to polysaccharides (*Streptococcus pneumoniae*) and protein antigens (tetanus toxoid). A patient may respond poorly to one or both types.

Specific antibody responses should be evaluated at baseline and post-immunisation, even if the baseline values are protective. When evaluating the post-vaccination

results, a response above the baseline is sought. A patient may respond poorly to protein and/or polysaccharide antigens.

If the antibody level is below the protective limit for Tetanus toxoid (<0.10IU/mL) after vaccination, an impaired response can be assumed. Some patients with common variable ID can produce protective antibodies to Tetanus toxoid, but still need IRT to protect against other bacterial infections.

A *S. pneumoniae* serotype-specific level of 1.3ug/mL has been considered to be protective following polysaccharide immunisation:

- An increase from baseline antibody values is always observed in immunocompetent patients, post-vaccination.
- In levels well below the protective level, fold is irrelevant. A response above the protective level is required.
- If the baseline level is >1.3ug/mL, a twofold response is considered to be acceptable.
- A normal response is additionally evaluated by determining the percentage of serotypes to which the patients responded: a protective response in more than 50% of the serotypes in children <6-years, with at least a twofold increase in the titers, or a protective response in more than 70% of the serotypes in patients >6-years, with at least a twofold increase in the titres.
- If a normal response is obtained, follow-up antibody levels are recommended in six months' time to assess the extent of waning of immunity. Waning of more than 50% of the serotypes in patients <6-years and in more than 70% of the serotypes in patients >6-years is regarded as abnormal.
- If a child >2-years old received the pneumococcal conjugate vaccine (Prevenar®), a level of 0.35ug/mL is considered protective. A twofold elevation in antibody titre post-vaccination should also be observed.

Recommendations

1. The goal of IRT is to provide protection from infections, prevent permanent end organ damage and restore/maintain good quality of life.
2. IRT (referring to IgG replacement by intravenous or subcutaneous administration) use is indicated in hypogammaglobulinaemia with low B cells.
3. IRT therapeutic use is indicated in hypogammaglobulinaemia with normal B cells and poor antigen specific antibody production.
4. IRT therapeutic use may be indicated in specific antibody deficiency.
5. IRT therapeutic use may be indicated in subclass IgG deficiency with specific antibody deficiency.
6. IRT therapeutic use is not indicated in THI or IgA deficiency
7. IRT may be indicated for recurrent, persistent, or invasive infections while an immune deficit is still being investigated
8. IRT alone does not restore mucosal immunity which is mediated by IgA.
9. With established end organ damage such as bronchiectasis, adjunctive antibiotic prophylaxis and other measures may be beneficial and required in addition.
10. A minimum IRT therapy trial of 12 months is required to document efficacy, allowing for seasonal variations.
11. For PID with absent B cells and severe antibody deficiency states, IRT at dosages required to prevent infections, is indicated lifelong, while there is no alternative therapy currently available.

References

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