Primary Immunodeficiency — Missed Opportunities and Treatment Challenges

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ABSTRACT
Primary immunodeficiencies (PIDs) are not as rare as previously thought. They usually manifest with increased susceptibility to infections but clinical manifestations are very variable. After exclusion of HIV, TB and other known risk factors and predisposing causes for recurrent infections, PIDs must be considered. A positive family history is the single most important alerting sign, but onset of symptoms may be delayed to adulthood. The National Health Laboratory Service (NHLS) provides a wide range of diagnostic services to 80% of South Africa’s population and private laboratories also offer immune testing. Most treatment options are available but awareness of PIDs in South Africa is poor, resulting in many diagnoses being missed and treatment delayed.

Early diagnosis and treatment prevent infectious complications and can achieve near-normal life expectancy. The treatment for PID is complex and varies according to the underlying defect. For B-cell-related disorders, which make up the largest group, and combined immunodeficiency, the mainstay of therapy is immunoglobulin (Ig) replacement intravenously (IVIG) or subcutaneously (SCIG). T-cell-related severe combined immunodeficiency (SCID) requires urgent immune reconstitution with stem cell transplant, supportive Ig and other therapy; innate disorders may require treatment with antibiotics, antifungals, cytokine replacement, vaccinations and also stem cell transplants.

Different social situations and access to health care present treatment challenges which require supportive as well as definitive options and an individualised approach.

INTRODUCTION
It is estimated that in Africa up to 900,000 people may have a primary immunodeficiency (PID), of whom only 1,000 are currently registered.1 Hence the large majority of patients with genetically based immunodeficiency remain undiagnosed and undertreated.

Most paediatricians, physicians and general practitioners, as well as ear, nose and throat (ENT) specialists, pulmonologists and haematologists, have probably been faced with a patient with suspected PID in the past year. This is especially relevant where the patient has severe, persistent, unusual or recurrent (SPUR) infections. When the common causes for secondary immunodeficiency in South Africa have been excluded, the diagnosis for a primary cause needs to be pursued as a matter of urgency – in the infant to prevent mortality and in the older child and adult to prevent significant morbidity and shortened life span, as most PIDs can be treated or improved.

BACKGROUND/Epidemiology
HIV affects about 10% of the South African population with an estimated 5.6 million people among its total population of 50 million living with HIV/AIDS.2 It is more difficult to obtain prevalence figures for other causes of secondary immunodeficiencies such as malnutrition and immunosuppression from other diseases or induced by drugs.

Antibody deficiencies or B-cell defects make up the largest portion of PIDs and of these the heterogeneous group of common variable immunodeficiency (CVID) is the most common according to international registries.3 Although Iga deficiency is the single most common primary deficiency, most affected individuals are asymptomatic in terms of recurrent infections. The European Society for Immunodeficiencies (ESID) registry currently has over 16,000 patients registered and is able to give valuable outcome data linked to the diagnosis, but also the delays.

The South African registry has 200 patients to date for an estimated minimum prevalence of at least 5,000.

South African Demographics – the SA PID Registry
The demographic details of the Primary Immunodeficiency Registry of South Africa (2008-2012) reflect predominantly diagnoses from the Western Cape region. Hence research bias is evident and conclusions cannot be generalised. They do however yield some informative experience on local PID patterns and gaps in care.

• Family history: A positive family history was found in 30% of patients, especially complement C5/6 deficiency (6/21) and hereditary angio-oedema (HAE) (30/39) but importantly also in severe combined immune deficiency (SCID) (3/7) and agammaglobulinaemia (7/16).

• Presenting symptoms: The single most common presentation was that of respiratory tract infections (42%).

• Referral pattern: 30% of patients were referred by paediatricians outside a tertiary centre, 15% were referred by a tertiary centre, 7% by physicians other than from a tertiary centre, 6% by general practitioners, 6% from secondary hospital level, and 3.5% were self-referred via the Primary Immunodeficiency Network of South Africa (PINSA).

A total of 58 patients with C5/6 deficiency and HAE were added to the registry from a tertiary medical facility; the primary referral pattern is not available.

• Province distribution: Western Cape 69%, Gauteng 14%, KZN 5%, Eastern Cape, Northern Cape, Free State and North West each <5%. The Northern Province/Limpopo registered no patients.

• Diagnostic categories: Diagnostic categories are shown in Figure 1 (according to the 2011 International Union for Immunodeficiency (IUIS) Criteria).4 Antibody-related (45%), phagocyte defects (6.4%), complement (31%), combined immunodeficiencies (4%), auto-inflammatories (4.5%), recognised syndromes (4%), innate (3.5%), non-definable diagnosis (2%).
6. 5/12 deaths were preventable with treatment (3 agammaglobulinaemia, 1 HAE, 1 C5 deficiency).

8. Recognition of the key signs for PID in the specific local regions/circumstances however needs to be identified. In South Africa these are dissemination of Bacille Calmette-Guérin (BCG), recurrent meningococcal infection, recurrent or atypical tuberculosis (TB).

REVIEW OF THE JEFFREY MODELL FOUNDATION (JMF) ‘10 WARNING SIGNS’
To identify the PID patient – and not miss opportunities

These alerting signs of PIDs based on expert opinion,5 have been published widely by many organisations and publications and they have no doubt helped identify thousands of patients. However there is little published literature on the comprehensive awareness for and effectiveness of these criteria in different regions of the world.6 In South Africa specifically it is also important where and at whom the awareness education should be targeted so that we do not miss the patient with PID. In regions with high prevalence of infectious diseases, the death of an infant or complications of infections such as bronchiectasis can all too easily be ascribed to the infectious organisms, while the underlying cause may be missed. Consanguinity is more prevalent in North African countries and the SA Asian population as a cause for SCID with excess of autosomal recessive inherited disorders, but family history is one of the single most important features in early diagnosis of PID overall. In South Africa like in other countries where BCG vaccine is given routinely at birth, the dissemination of BCG in the HIV-negative infant is an early and serious warning sign of severe immunodeficiency.

1. >4 new ear infections within 1 year: this may not be an uncommon feature in infants who are placed in crowded day or home care and in those where atopy is not managed optimally.

2. >2 serious sinus infections within 1 year: the access to health care and correct use of antibiotics has to be taken into account in disadvantaged communities as a risk factor.

3. >2 months of oral antibiotic treatment with little effect: risk factors mentioned under (1) and (2) have to be taken into account here, as well as the indiscriminate use of antibiotics, and the patient history of a frequent change of doctors or clinics where a dedicated primary doctor is not part of the healthcare structure.

4. >2 episodes of pneumonia within 1 year: this in the absence of predisposing risk factors such as foreign bodies, cystic fibrosis and respiratory complications after birth in the absence of HIV can be an important alerting sign.

5. Failure of an infant to gain weight or grow normally: this, although a very important sign, may not become a feature until later in infancy even in SCID.

6. Recurrent, deep-skin or organ abscesses: impetigo and superficial abscesses in the absence of an identified PID are not uncommon in the lower socioeconomic environment patient or with neglected or severe eczema. A hepatic abscess however, especially with granuloma formation where acid-fast bacilli cannot be isolated should immediately alert to PID related to neutrophil dysfunction, in particular CGD.

7. Persistent thrush in the mouth or fungal infections of the skin.
8. Need for intravenous antibiotics to clear infections: this has been identified as one of the 3 key alerting signs for PID especially relating to neutrophil defects.

9. >2 deep-seated infections, including septicaemias: children or adults presenting with recurrent meningococcal disease in South Africa especially in the Cape regions should be investigated for complement deficiencies at least with the cost-effective total complement assay.

10. A family history of PID: this is the single most important feature in early identification of patients with PID especially in those (but not only) with recurrent or severe infections. Congenital anomalies may further alert to the presence of a PID, e.g. in the case of DiGeorge syndrome.

Of the above (i) a family history for PID; (ii) use of intravenous antibiotics to treat sepsis; and (iii) failure to thrive in T-lymphocyte PID were the warning signs found to be most predictive of PID in children in a study by Subbarayan et al.9

In South Africa specifically a child should be referred for investigation for PID after exclusion of HIV and TB by the recommended IMCI approach (Integrated Management of Childhood Illness)8 where there is persistence of infections, specific warning signs and/or clinical features (see Table 3, Suchard et al., current edition), and after exclusion of atopy.

Several excellent reviews of the clinical recognition of PID are available in the published literature including two recent contributions from South Africa.9,11

TREATMENT CHALLENGES
With appropriate prophylaxis, optimised immunoglobulin (Ig) replacement and more successful outcomes for transplantation the number of PID patients who survive to adulthood is growing. Appropriate treatment is directed by correct and timely diagnosis. Prevention of and prompt treatment of infections, most commonly of the respiratory tract, are the cornerstone of care. Treatment should be monitored by a dedicated physician team. Table I outlines the treatment.

Prevention and treatment of infections

Treatment of the current infection is the first step in PID management; it depends on the causative aetiological agent and the specific deficiency of the immune system.

Prophylactic antibiotics are one of the mainstays of treatment for PID. Controlled studies are lacking on the preferred method of prophylactic antibiotic use in PID generally. Hence current regimens are based on experience with other diseases such as otitis media or cystic fibrosis. These include sulfisoxazole, amoxicillin, trimethoprim-sulfamethoxazole (TMP-SMX) and azithromycin. Emergence of resistance has been minimal in these studies and antibiotic prophylaxis in PID is generally guided by the microbial pathogens observed.12 A twice- or three-times-weekly dosing regimen given as a once-daily dose is recommended for prophylaxis. Penicillin prophylaxis is effective in meningococcal prophylaxis.

The efficacy of antimicrobial prophylaxis for specific PIDs such as CGD with TMP-SMX 6 mg TMP/kg/d and itraconazole 5 mg/kg/d has been documented in systematic studies.12 Azithromycin through its anti-inflammatory actions may improve lung function and decrease exacerbations in bronchiectasis, a condition which many patients with antibody deficiency still develop despite Ig replacement.

Boosting of the immune system

Ig replacement

Ig replacement is the mainstay of treatment for antibody deficiency. In South Africa the intravenous form of immune globulin (IVIG) is the usual method of administration for replacement therapy in PID. Several safe and effective Ig products registered for IV (e.g. Polygam, Intragam, Octagam) and subcutaneous administration (Beriglobin) are currently available in South Africa from local donor pools and overseas plasma sources. There is no place for the use of intramuscular injection (IMI) administration in antibody or other PIDs.

As these are biological products with limited availability, they should be prescribed for the correct indications.

A growing number of diseases are being treated with Ig replacement including those responding to immune modulation. Increasing use of Ig for neurological diseases threatens the sustainability of supply for patients with PID indications for whom there is no alternative effective treatment. Although potentially beneficial, these uses are not approved in countries where there are regulatory bodies. In South Africa, medical literature, clinical consensus and individual decisions determine the motivation for Ig use.

The most recently published (2012, 2nd edition, National Blood Authority of Australia) ‘Criteria for the clinical use of intravenous immunoglobulin in Australia’ provides useful information and recommendations on the use of IVIG treatment. These criteria are not absolute practice guidelines and each patient should be individually assessed for treatment.14

Antibody deficiency key diagnoses for evaluation of Ig replacement include agammaglobulinaemia, CVID, SCID, Wiskott-Aldrich syndrome for which IVIG has an established therapeutic role as Ig-replacement therapy with high level of evidence.

<table>
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<th>Table I. Treatment of PID</th>
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<td>Prevention and treatment of infections, e.g. antibiotics</td>
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<td>Boosting of the immune system, e.g. gammaglobulin (Ig) therapy both intravenous (IVIG) and subcutaneous (SCIG), vaccinations, gamma interferon, growth factors, e.g. granulocyte-macrophage colony-stimulating factors</td>
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<td>Treatment of the underlying cause of the immune deficiency, e.g. haematopoietic stem cell transplantation, gene therapy, enzyme replacement</td>
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<td>Treatment of associated conditions: autoimmune disorders and malignancy, e.g. anti-inflammatories and immune modulators</td>
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Guidelines for dosage recommend 400-600 mg/kg IVIG every 3-4 weeks, or 100 mg/kg SCIG every week – but clinical outcome measurements defined by frequency and severity of infections should determine the individualised optimum dose for each patient. Trough serum levels of IgG generally aimed at above minimum serum levels recommended for age are adjuncts in the assessment but are not the sole or deciding criteria on Ig dosage. A steady state can be expected after about 3 months of regular therapy.

The members of the American Academy of Allergy Asthma and Immunology (AAAAI) outline eight useful guiding principles for the safe, effective and appropriate use of IVIG for PID with the ‘goal to render the patient infection free, to the greatest extent possible’ and with the aim to ‘preserve organ function, improve quality of life, prevent infection-related death and increase lifespan.’ Table II lists adapted guidelines.

Increasingly the subcutaneous route (Fig. 2) is chosen for Ig therapy and it has become standard for Ig replacement in European countries such as Sweden. Interestingly the first patient diagnosed with agammaglobulinaemia was successfully treated by the subcutaneous route by Ogden Bruton. The major advantages include virtual absence of systemic side-effects, venous access is not required and more even serum levels of Ig with higher trough levels are achieved.

A study by Gardulf and Borte following 10 months of weekly self-administered SCIG infusions at home showed that SCIG home therapy was associated with significant improvements in health-related quality of life (HRQL) measurements and treatment satisfaction (TS), particularly in patients who had previously received IVIG therapy in hospital settings.

Ultimately the decision regarding the modality of Ig replacement should be individualised to suit patient preference and treatment goals.

### Vaccinations

Childhood vaccinations are aimed at enhancing safe endogenous Ig production which should also be pursued in PID unless significant T-cell deficiency is suspected. Vaccination with protein and polysaccharide antigens is routinely used to assess effective antibody production.

The use of licensed vaccines outside the paediatric immunisation schedule, as well as influenza vaccinations, is part of the treatment of PID patients but guidelines on the optimal use require further research. Hence the risks and benefits must be assessed for individual patients.

In T-cell deficiency live viral vaccines such as BCG must be withheld, as also in the neonate with a family history of severe immunodeficiency. Enhanced immunisation of family members and caregivers of PID patients is recommended.

A useful overview on vaccinations in PID by Cant can be downloaded from www.ipopi.org/uploads/media/pastevents/presentations/PIDandvaccines (Oct 2010).

### Interferon-gamma

This macrophage-activating cytokine produced by T cells and natural killer cells appears to be beneficial in a subgroup of CGD with recurrent infections; the expense prohibits general use in CGD patients.

### Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is discussed in a separate article in this journal. The outcome and patient survival after HSCT has seen tremendous improvements in recent years.

### Gene therapy

Disease-related genes have been identified for most of the PIDs and there are realistic limitations for HSCT with the lack of availability of donors and serious adverse events to the procedure. Based on the results of clinical trials gene therapy has become a feasible option for treatment of some of the severe forms of T-cell related PID (X-linked SCID and adenosine deaminase deficiency). Tragically ‘first-generation’

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**Table II. AAAAI Guiding Principles for IVIG in PID (adapted)**

- **Indication** – IVIG therapy is indicated as replacement therapy for patients with PID characterised by absent or deficient antibody production. This is an FDA-approved indication for IVIG, for which all currently available products are licensed.
- **Diagnoses** – there are a large number of PID diagnoses for which IVIG is indicated and recommended. Many have low total levels of IgG, but some have a normal level with documented specific antibody deficiency.
- **Frequency of IVIG treatment** – IVIG is indicated as continuous replacement therapy for PID. Treatment should not be interrupted once a definitive diagnosis has been established.
- **Dose** – IVIG is indicated for patients with PID at a starting dose of 400-600 mg/kg every 3-4 weeks. Less frequent treatment, or use of lower doses, is not substantiated by clinical data.
- **IgG trough levels** – IgG trough levels can be useful in some diagnoses to guide care but are NOT useful in many and should NOT be a consideration in access to IVIG therapy.
- **Site of care** – the decision to infuse IVIG in a hospital, hospital outpatient, community office, or home setting must be based upon clinical characteristics of the patient.
- **Route** – route of immunoglobulin administration must be based upon patient characteristics. The majority of patients are appropriate for intravenous, and a subset for subcutaneous, therapy.
- **Product** – IVIG is not a generic drug and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to ensure patient safety. A change of IVIG product should occur only with the active participation of the prescribing physician.
retroviral vectors also caused leukaemia in some patients through transactivation of oncogenes. Since deletion of the responsible elements from the vectors, safe and effective gene therapy is emerging as a promising treatment option for PID. Human stem cell production from other cell sources has recently been achieved with human fibroblasts giving rise to further promising developments in gene therapy.18

TREATMENT OF THE ASSOCIATED CONDITIONS

The treatment of inflammatory complications in CGD is discussed further by Seger.13

TAKE-HOME MESSAGES

• Although regional differences exist, with the exception of IgA deficiency (prevalence 1 in 300-500), PIDs are more common than is generally believed with a 1 in 1 200 prevalence.
• PID education must be aimed at paediatricians/physicians and awareness must be raised among the public and targeted to meet the specific and unique needs of a region or country.
• The clinical presentations of PID are very variable, but usually manifest with an increased susceptibility to infections especially of the respiratory tract. This must be interpreted against the background and in the context of a high prevalence of infectious diseases and very diverse social backgrounds.
• PID should be suspected in the patient with a family history of PID, with the need for IVI antibiotics to clear infections, >2 cases of pneumonia in 1 year, BCG dissemination in an HIV-negative infant and a liver abscess in childhood.
• Genetic counselling is an integral part of PID patient management.
• SCID is a medical emergency!
• Appropriate treatment with a choice of options for Ig replacement must be individualised and monitored for infection-free survival and quality of life.

Acknowledgement

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Declaration of conflict of interests

Dr Monika Esser works for the Immunology Unit Tygerberg, National Health Laboratory Service, Stellenbosch University, which offers diagnostic testing for primary immune deficiency. Secretarial support is received from National Bioproducts for maintaining the South African Primary Immunodeficiency Register.

REFERENCES