

## Immune Modulation in Children. A South African Perspective

Pieter Rousseau Fourie\*

Department of Mechanical and Mechatronic Engineering, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa

\*Corresponding author: Pieter Rousseau Fourie, Department of Anesthesiology and Critical Care, Faculty of Medicine and Health Sciences, P.O. Box 241, Cape Town 8000, South Africa, Tel: +27-8084249; Mob: +27-825511845; E-mail: [prfourie@sun.ac.za](mailto:prfourie@sun.ac.za)

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### Abstract

Immune deficiencies in South Africa can be divided into two categories, i.e. primary immune deficiencies or secondary due to illnesses such as malignancies or infection e.g. the human immune virus (HIV). In the private pediatric clinical setting, children of-ten present with illnesses that can be traced to selective secondary immune deficiencies. Although highly effective, not all children are eligible for intravenous immunoglobulin therapy, either due to costs or non-IgG related immune deficiencies such as selective IgA or T-cell deficiencies. Intramuscular and subdermal immunoglobulin options are equally expensive and uncomfortable. The use of oral immune modulators, such as the erythromycin derivatives, has raised some concern, mainly because of the potential risk of bacterial resistance. Other so called immune boosters, e.g. Echinacea's, are being advertised as potential solutions but have yet to prove to be efficient. In addition to this, the interaction between the gut micro-biome and the immune system is complex, but critical in maintaining and optimizing the immune system. Under certain disease entities such as inflammatory bowel disease, resulting in a leaky gut, the immune system becomes compromised because of the interaction between certain inflammatory signals and the lymphoid and bone marrow tissue specifically the naive and memory T-cell populations, such as CD4 and CD8 lymphocytes. An overview to immune modulation will be presented that has a direct beneficial effect on the health outcome of the children and new therapeutic modalities will be evaluated in terms of their response and restoration of the T-cell populations.

**Keywords:** Immune modulation; IVI immunoglobulins; Hygiene theory

### Background

The immune regulatory scene has changed dramatically since the 1994 with the arrival of the human immunodeficiency virus (HIV). Especially in Southern Africa with the high incidence of tuberculosis (TB), the management of immune compromised children, with underlying HIV and TB, has become one of the main focus points in the fight against infective diseases. Moreover, overcrowding, pollution and poor sanitary conditions as all part of the rapid urbanization in South African cities have led to an environmental strain that resulted in the high incidence of immune disorders [1]. Westernized life style including a diet high in preservatives and colorants added insult to injury [2].

With a total population topping almost 50 million, and the wealth inequalities of the past, South Africa can be divided into mainly two groups. Firstly, numbering about 8 million, an affluent, mainly white middle class with access to private healthcare. The latter comprises of around 240 privately owned hospitals and, provided one belongs to a private medical fund, access to excellent medical care and support is offered. Secondly a very large, mostly black population living in overcrowded and often appalling conditions, poor sanitation and drinking water, is exposed to serious pathogens such as TB and HIV [3].

In addition, the diverse ecosystem in Southern Africa results in an abnormally high allergenic environmental load (the fynbos ecosystem alone contributes to more than 3500 plant species) resulting in a high incidence of allergic complaints such as allergic rhinitis and asthma.

The addition of the allergic component to an already compromised immune system would then theoretically lead to a dramatic increase in children suffering from primary immune deficiency disorders (PID) [4].

The over- and misuse of antibiotics worldwide, and definitely in South Africa, should finally sway the balance, as defined by the hygiene theory, towards a complete deranged immune system primed for havoc on the infectious agents arena [5].

### Hygiene Theory

Although highly effective, not all children are eligible for intravenous immunoglobulin therapy, either due to costs or non-IgG related immune deficiencies such as selective IgA or T-cell deficiencies. See Table 1. Intramuscular and sub-dermal immunoglobulin options are equally expensive and uncomfortable. Surprisingly, the incidence of PID illnesses in South Africa is exceptionally low. This can either be ascribed to poor statistical data, losing a large number to children with HIV and TB, or otherwise it could imply that in South Africa the low incidence of PID could be ascribed to the hygiene theory after all [6]. A study by Lawrie and co-workers confirmed that the pediatric immunohematological reference intervals for full blood count and lymphocyte subsets in South African children are similar to those of international reference intervals [7]. In a more recent, yet unpublished study, Payne et al. compared a subset of children living in the so called poor communities in South Africa to children from a more affluent community. What transpired was that the children from the more affluent community demonstrated a statistical difference in the T-cell subsets, i.e. lower values, than their poor community counterparts. The ratio of naïve-to-memory CD4 and CD8 T-cells reaches a 1:1 ratio shortly after the first year of life in healthy South Africa children [8].

This is far earlier than studies from resource-rich countries, where it occurs only during the third or fourth year of life. An increased proportion of natural killer cells and activated T-cells were also found compared to studies in the US and Europe as well as in the more affluent South African pediatric population. The marked difference observed in these and other parameters are important in understanding the developing pediatric immune system within an African, poorly resourced context but at the same time rendering an explanation why children in the more affluent areas

Patient	IgG (pre-treatment) G/l	IgG (post-treatment) G/l
1	5.71	10.2
2	3.44	5.62
3	3.3	4.9
4	6.29	10.4
5	3.77	8.38

**Table 1:** Blood results of 5 patient’s response to IVI immunoglobulin therapy (IgG fluctuate according to age, therefore no normal reference values were included): Post-treatment after one month. All immunoglobulin values were obtained using the nephelometric method (Image: Beckmann).

### Immune Compromised Conditions Combining T-cell and Immunoglobulin Deficiencies

The challenge arises where a child, from the more affluent community, presents with a history of recurrent infections and the immune profile does not always match the set criteria of the medical aid to institute intravenous immunoglobulin replacement therapy or when it is not effective [9,10]. Table 2 demonstrates the results from a number of children from my clinic with a wide variety of immune disorder conditions, some which do not meet the international criteria for immunoglobulin replacement therapy yet at the same time rendering the patient highly susceptible to infections, both viral and bacteria. What is important to note is the low CD4 and CD8 counts that is a consistent find throughout the group.

Compared to a match group of “normal” children from the same population subset, see Table 3, the CD4 and CD8 counts were significantly less. The immunoglobulin levels e.g. IgM, IgG, IgA and the IgG sub-fractions fluctuated with eight of the children demonstrating selective immune deficiency and six normal. Some of the former group were eligible for IVI immunoglobulin therapy although their medical aids did not support this. On the other hand, four of these children in fact did receive IVI immunoglobulin therapy but they reverted back to low IgG values after cessation of the IVI immunoglobulin therapy program. Their susceptibility to infections increased again suggesting that the CD4 and CD8 levels might be the main contributing factor to their low resistance.

Patient	Diagnosis	CD4 1000-1800 cells/µl	CD8 800-1500 cells/µl	Age (years)	IgM 0.5-2.5 G/l	IgA 0.6-3.0 G/l	IgG 7.0-16.0 G/l	IgG1 3.77-11.31 G/l	IgG2 0.68-3.88 G/l	IgG3 0.16-0.89 G/l	IgG4 0.01-1.70 G/l	Ethnicity
1	Unclassified Combined Immune Deficiency	552	197	7	1.32	0.54	6.42	4.74	0.66	0.17	0.78	Caucasian
2	Unclassified Combined Immune Deficiency	421	558	9	4.26			4.51	2.02	0.29	3.01	Caucasian
3	Unclassified Combined Immune Deficiency	568	275	11	0.95	0.33	6.14	4.37	1.23	0.25	0.15	Caucasian
4	CVID	935	684	8	0.4	0.22	3.89	2.86	0.77	0.3	0.1	Caucasian
5	Unclassified Combined Immune Deficiency	853	396	4	0.58	0.41	5.42	4.56	0.6	0.28	0.1	Caucasian
6	Unclassified Syndrome, Immune Deficiency	391	190	5	1.47	0.46	9.62	5.86	1.32	0.4	0.04	Caucasian
7	Unclassified Combined Immune Deficiency	346	300	11	1.97	0.71	11.7	7.84	1.18	0.28	0.31	Caucasian
8	Unclassified Syndrome, Immune Deficiency	941	557	5	2.92	1.75	15.1	16.7	2.23	0.51	0.33	Caucasian

9	Unclassified Syndrome, Immune Deficiency	413	542	4	0.35	0.63	3.46	3.26	0.66	0.18	0.477	Caucasian
10	SCID (malignancy) plus	24	35	9	0.54	0.36	7.6	5.95	1.56	1.36	0.19	Caucasian
11	CVID	607	585	7	1.11	0.54	5.55	3.49	0.96	0.34	0.16	Caucasian
12	Immune Deficiency	102	65	1	0.55	0.33	3.44	2.48	0.54	0.44	0.12	Caucasian
13	MEGDEL syndrome, Immune Deficiency	417	633	7	1.92	0.64	7.81	4.98	2.24	0.23	0.55	Caucasian
14	Immune Deficiency	921	571	9	0.78	0.69	6.16	4.71	0.4	0.28	0.01	Caucasian

**Table 2:** Blood results for 14 patients presenting with recurrent infections: All CD4 and CD8 values were derived using the flow cytometry technique (Aquiios, Beckmann Coulter).

Patient	CD4 1000-1800 cells/ $\mu$ L	CD8 800-1500 cells/ $\mu$ L	IgG G/l
1	1522	1363	7.93
2	3796	1392	5.92
3	1904	1821	8.07
4	1158	968	8.06
5	2749	1426	8.37

**Table 3:** Blood results for 5 normal children. (IgG fluctuate according to age, therefore no normal reference values were included).

A number of options exist that could be offered to the patient.

### Plant phyto-chemicals

The so called Echinacea's have been thought to potentiate the immune system but an extensive Cochrane review published in 2014 could not demonstrate any significant beneficial effect [11].

Curcumin has been demonstrated to have some beneficial "immune saving" effect in patients that receive radiation therapy whereas cinnamaldehyde (alpha-beta-unsaturated carbonyl group) interferes with TLR4, increases proliferation of splenic lymphocytes and subsequently the activation of macrophages leading to an increased nitric oxide production. Supported by an increase in IL-1beta, IL-6, IL-15 and IFN-gamma [12].

### Antibiotic prophylaxis

The use of certain classes of antibiotics at half therapeutic dosages is well known. The macrolides results in a marked reduction of cytokine levels in sputum and plasma levels. The Interferon-gamma/interleuken-4 ratio increases whereby the inflammatory response is down regulated (IL-1, IL-2, IL-5 and TNF-alpha decreased) together

with a class switch from a Th2 to Th1 response, which is probably the mechanism whereby the immune system is optimized [13].

Recently there has been some debate regarding the increase in resistance to the macrolide family of antibiotics, although at the level of half therapeutic dosage, it is unlikely to cause any serious resistance. It has been demonstrated to be inexpensive yet some concern regarding its safety with long term use is now coming to the fore [14].

### Interferon alpha 2b

Interferon is effective in boosting the immune system, but because of its potential side effects, the route of administration as well as the cost the product fell into disrepute [15].

### Parasites

Parasites, through associated molecule patterns, stimulates T-cells and the release of IFN-gamma. On the other hand, during a malaria infection, T-reg inhibition of CD8 T-cells will prevent the malaria parasite from being eradicated [16].

During a schistosoma infection the immune system is deranged and, depending on the host response, the immune system of the host could realize into one of three options, i.e. uncontrolled Th1, a modified Th2 and lastly a balanced Th1/Th2 response. Thus it results in complex immune environment with the response to medication often unsatisfactorily and the host developing a synergistic relationship with the parasite.

Thus the role of parasites in modifying the immune system is complex and unreliable in terms of the hygiene theory [17].

### The gut micro-biota

The intestinal microbiota and the gut immune system communicates on a constant opposing platforms in order to balance out a position of immune activation and tolerance. Chronic inflammation in the gut milieu is the result of a number of potentiating factors such as diet, environmental factors such as pollution, overcrowding (urbanization), infections and inherited gene

polymorphisms. Its potential detrimental effect is widespread and lymphoma, diabetes, Crohn's disease and ulcerative colitis are but a few of the devastating illnesses that can result from the mismatch between these two opposing giants [18-20].

## New Horizons

The challenge would therefore be to improve the T-cell population in its effectiveness and numbers. One such drug with a surprising benefit in terms of its effectiveness and mode of operation is the NPiS40, an immune response modifier (Ethogen Biotech). Derived and isolated from mammalian, ICPF is a single chain Nano-peptide of about 8kD long [21,22]. It acts similar to a biologic and as a biologic response modifier, it releases IL-6 early in the timeline resulting in an increase IL-2 expression which again acts as a growth factor/activator for T-cells, Natural killer-cells, and B-cells and the release of interferon-gamma [23]. Effectively this leads to an up-regulation of the cytotoxic and phagocytic immune cells, macrophage activation, NK-cell activation and acute phase protein production, all aimed at optimizing the innate immune system and rendering the humoral immune system more effective by facilitating the presentation of bacterial antigens to the T-cells and finally to the B-cells for immunoglobulin production [24].

After administering NPiS40 at 328 mg/ml, 1.5 ml S/C every third day for one month, the CD4 and CD8 levels increased to 198 cells/ $\mu$ l and 483 cells/ $\mu$ l respectively (refer to Table 2).

Another method that is gaining more and more acceptance, whereby the immune system can be modulated, is the radiation of blood applying ultra-violet radiation, the so called photoluminescence therapy. By indirectly oxidizing blood, the immune system is activated via the release of oxygen radicals and whereby the growth of fungi and viruses is inhibited. Furthermore the immune modulation that is brought about can indirectly improve the immune status [25].

## Summary

Immune modulation in children remains a challenge in as much that the present modes of modulation is either very successful or limited and very expensive. Also, the most common method applied, i.e. immunoglobulin replacement therapy is not effective in selective IgA deficiency as well as in CD4 and CD8 deficiencies. The new and novel options such as the UV radiation as well as the use of immune response modifiers (e.g. NPiS40) look very promising and should be investigated further.

## Conflict of Interest:

None

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