



UNIVERSITEIT•STELLENBOSCH•UNIVERSITY
jou kennisvenoot • your knowledge partner

Immune Modulation in Children in South Africa: a Practical Approach

Pieter Rousseau Fourie

28 September 2015



Fakulteit Geneeskunde en Gesondheidswetenskappe

Faculty of Medicine and Health Sciences





Topics



- Background
- Problem Statement
- Case Studies 1,2 & 3
- Underlying Immune Derangement
- Immune Modulation: Present
- Hygiene Hypothesis: A New Perspective
- New Horizons
- Epilogue

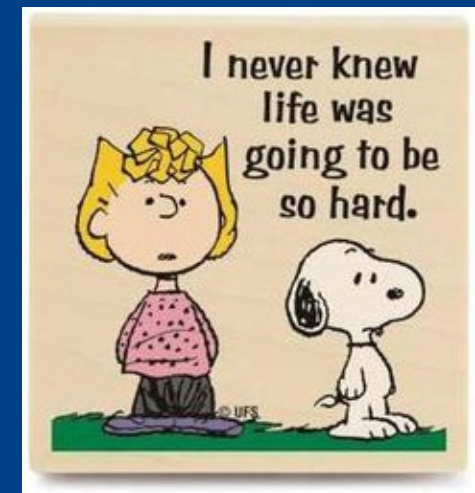




- 9 Billion People by 2050
- Urbanization, Overcrowding, Pollution, Day Care Centers: Shift towards Th2
- Westernized Lifestyle and Diet: Preservatives and Colourants
- Over- and Misuse of Antibiotics: Suppression of Th1
- South Africa: 49 Million; Developing Country with a very Diverse Population
 - Affluent, mostly White Middle Class with Access to Private Health Care
 - Poor, mostly Black, Living in Over Crowded Conditions and Exposed to Pathogens
 - TB & HIV: Low CD4 and CD8 Levels
 - Primary Immune Deficiency: Low Percentage
 - Weather and Diverse Ecosystems: Highly Allergenic Environment.



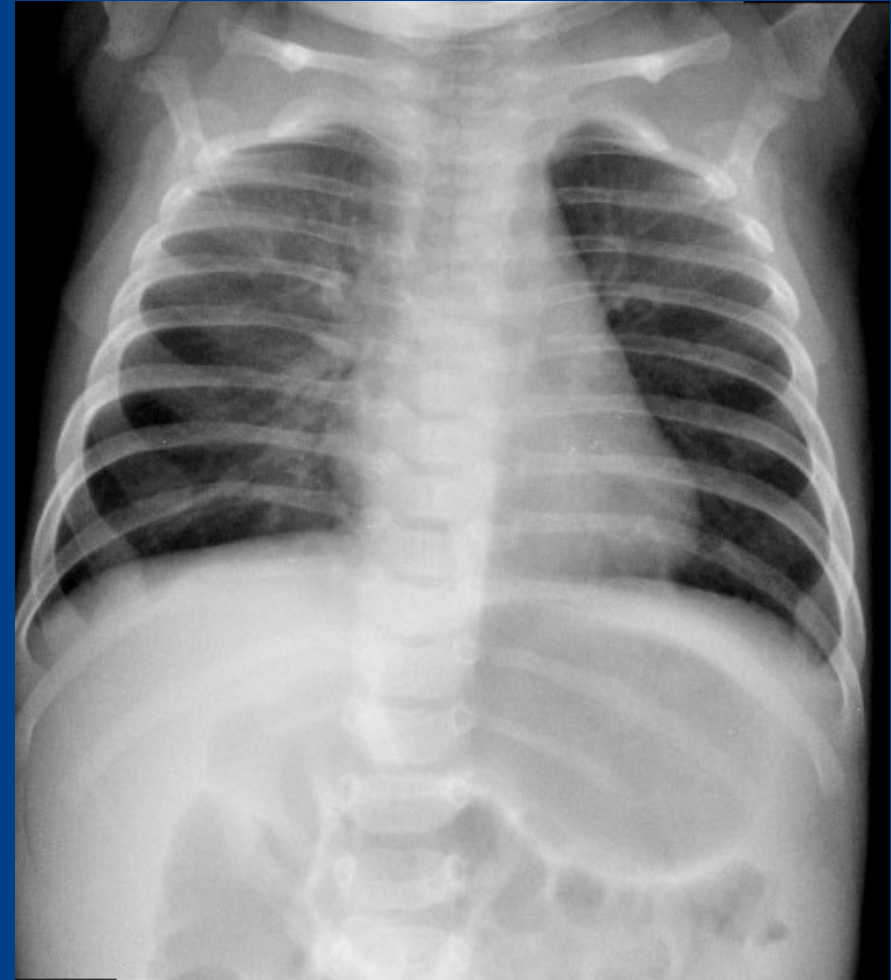
- A Number of Clinical Entities where the Immune System is Compromised
- Criteria According to the Definition of Primary Immune Deficiencies do not Hold
- Therapeutic Modalities such as IVIG, Prophylactic Antibiotics and Nutraceuticals " Immune Boosters" not Approved or Ineffective
- Leads to Repeat Prescription of Antibiotics or Hospitalizations
- Burden on the State and Private Health Care
- Emotional, Physical and Economical Impact





Case I

- 3 Months Baby Girl
- Tachypnoea, Distressed
- Failure to Thrive
- Xray: Bilateral Bronchial Infiltrates
- P. Jiroveci: Positive
- HIV: Negative
- TB: Negative





- Immunophenotyping Normal (Including Naive and Memory Cells as well as Beta/Gamma Delta T Cell Receptors were Normal)

- IgA: 0.10 (0.08-0.6 g/L)
- IgG: **2.08** (2.40-8.8 g/L)
- IgM: 0.39 (0.2-1.00 g/L)
- IgG1: **1.16** (1.51-7.92 g/L)



- Sulfamethoxazole & Trimethoprim
- IVIG @ 0.6g/kg Every 4 Weeks



Case 2



- 4 Year Old Girl
- One week old: Severely Distressed, Cyanotic
- Total Anomalous Pulmonary Venous Drainage
- Surgically Corrected
- No Dysmorphism
- Longstanding History of Recurrent Upper and Lower Respiratory Tract Infection.
- Multiple Hospitalizations





Case 2: Continue



- IgA Low
- CD4: 248/ccm & CD8: 425/ccm
- HIV & TB: Negative
- Ca⁺⁺ Normal
- Di George phenotype: Negative
- IgG against Haemophilus Low
- Medical Aid Refused IVIG
- Prophylactic Clathromycin @ Half Therapeutic Dose.

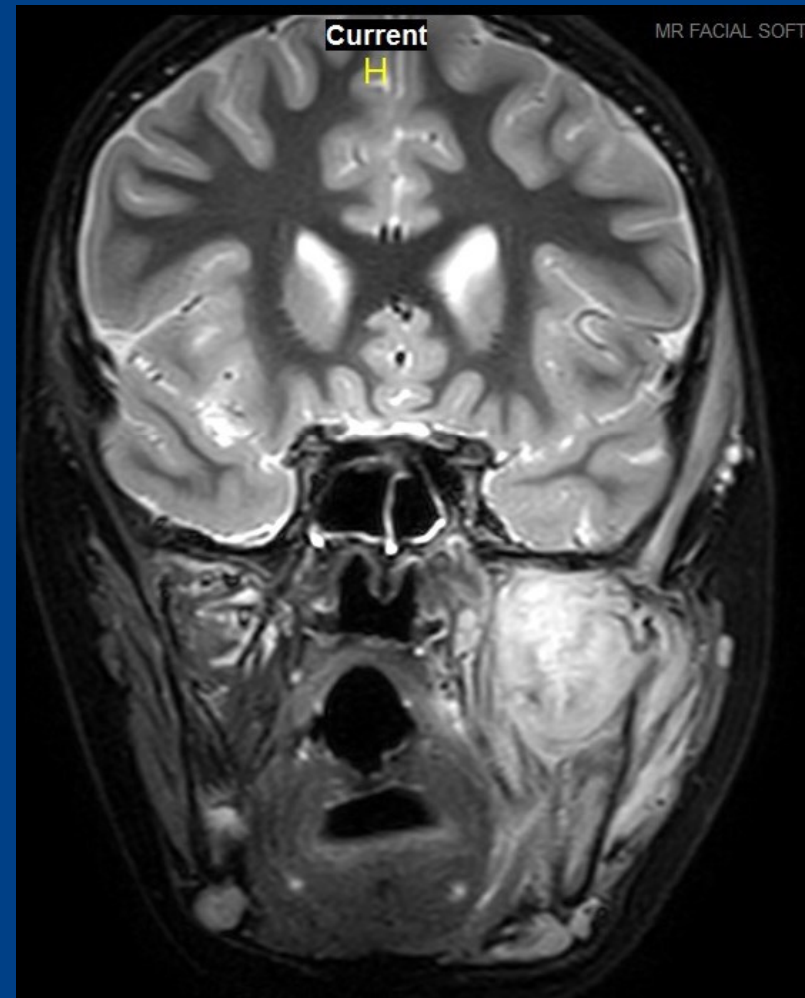




Case 3



- 9 Year Old Boy
- Slow Onset of Trismus
- Local Swelling over L Mandible
- Rhabdomyosarcoma
- Chemotherapy & Radiation
- After Six Months of Regression
- Sudden Expansion



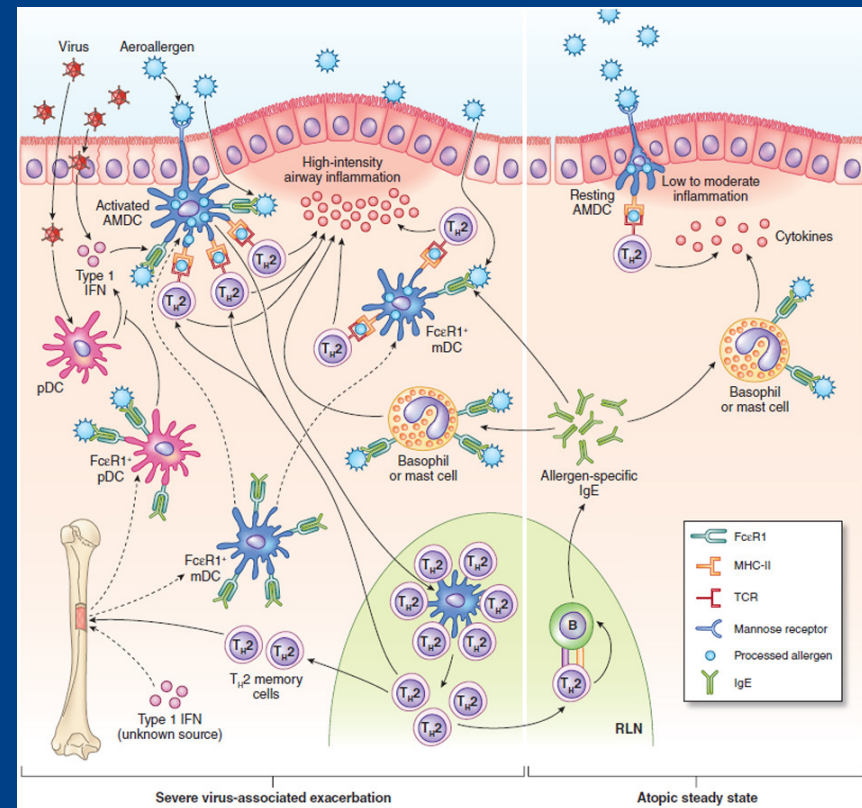


Case 3: Continue



- IgG: 6.98 (7-16 g/L)
- IgA: 0.41 (0.6-3.00 g/L)
- Complement C3 2.13 (0.55-1.2 g/L)
- Complement C4 0.51 (0.20-0.50 g/L)
- Total T-cell count 66 (1400-2000/cmm)
- CD4+ cell count 24 (700-1100/ccm)
- CD8+ cell count 35 (600-800/ccm)
- Total B cells 1 (279-860 cells/ul)
- NK cells 19 (100-480 cells/ul)
- CD4/CD45 Naive 2 (320-1000 cells/ul)
- CD4/CD45 Memory 16 (230-630 cells/ul)
- CD8/CD45 Naive 20 (310-900 cells/ul)
- CD8/CD45 Memory 9 (70-390 cells/ul)

- Immunoglobulin Replacement Therapy





Case 3: Underlying Immune Derangement



Escaping Immunosurveillance through TGFbeta Increase Leading to an Increase in Chemokine (C-C) Motif Ligand 2 (CCL2). The Latter recruits Myeloid Derived Suppressor Cells, Reduces Tcell Activation, Blocks Tcells and Suppresses the Tumor Micro-Environment (TME)

Activated Stat3 inhibits the Expression of Mediators necessary for Immune Activation Against Tumor Cells. Stat3 Promotes the Products of Immune Suppressive Factor, Alternating Gene Expression and Restraining Anti- Tumor Immune Responses

Xie, Oncoimmunology 3; June 2014

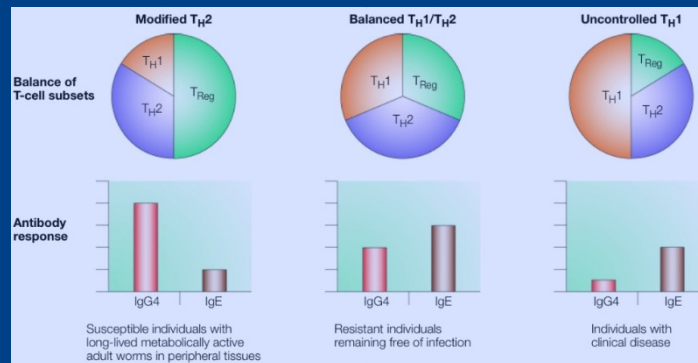
Pang et al, Cancer Discovery 2013; 3:936-51



Associated Molecule Patterns Stimulates T-Lymphocytes
and the Release of IFN-gamma

Treg Inhibition of CD8 T cell Responses during Malaria Infection

Immunology of Human Infections by *Schistosoma Mansoni*



Urban & Roberts: J. Exp. Med. Vol. 197. 2003

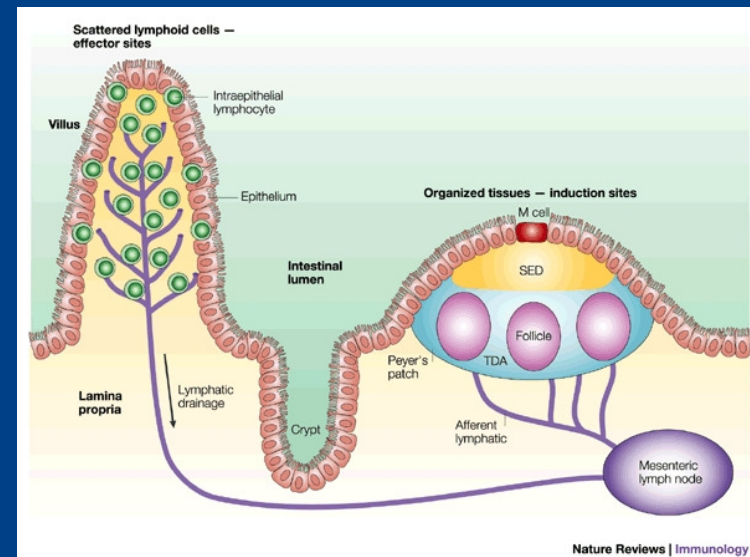
Nature Reviews, Immunology, Vol. 3, 2003



Immune Modulation: Gut Commensal Bacteria



- 3 Trillion bacteria
- Stimulates Gut Associative Lymphoid Tissue (GALT)
- Several Cytokines: TLR2&4
- Enhances Nitric Oxide Production
- Increases Phagocytosis
- by Peripheral Blood Macrophages
- Probiotics





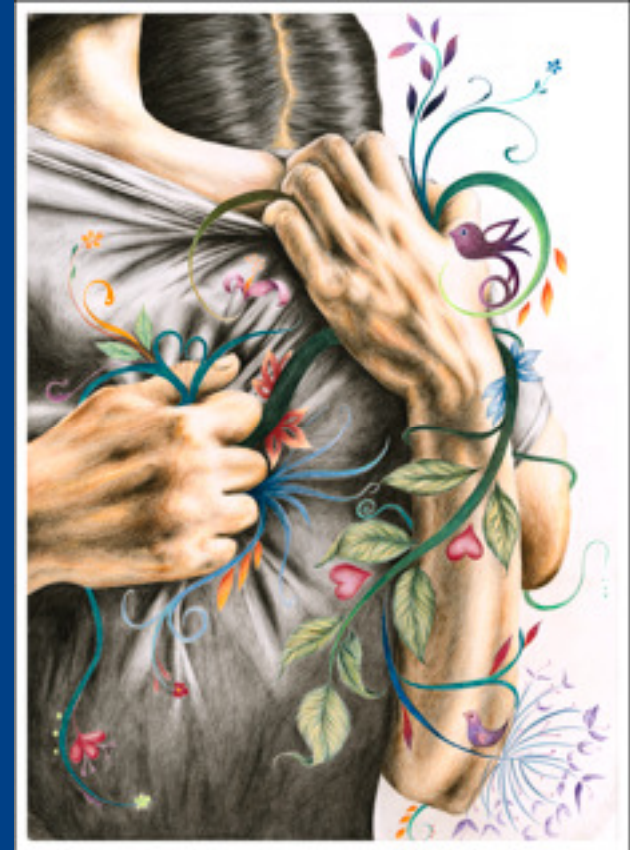
Curcumin :

Radiation Therapy

Cinnamaldehyde :

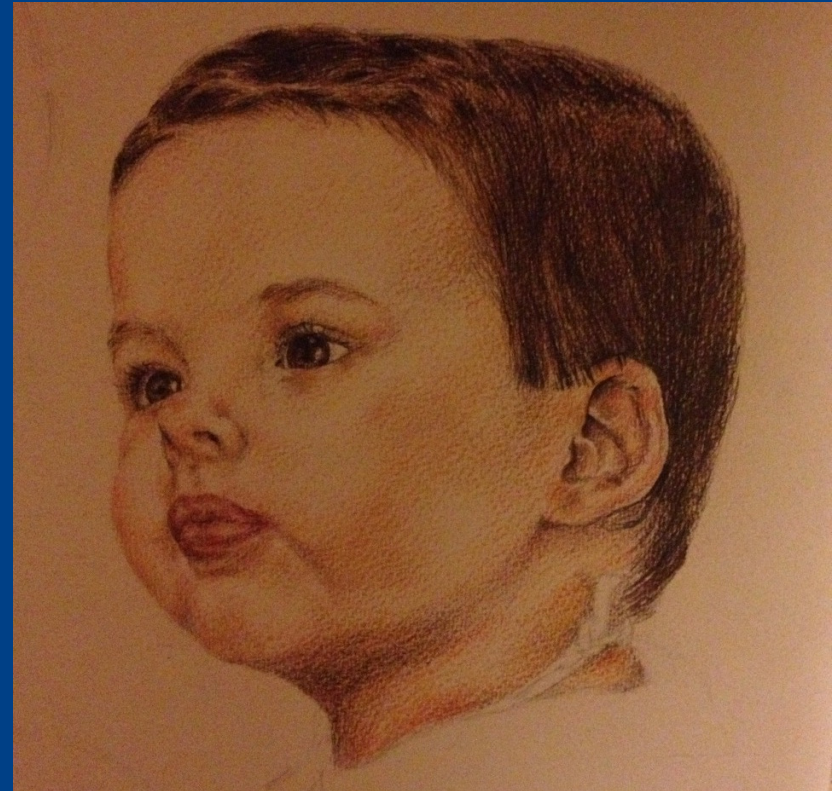
(alpha-beta-unsaturated carbonyl group)

- Interferes with TLR4
- Inhibition NOD2
- Increased Proliferation of Splenic Lymphocytes
- Activation of Macrophages & Increased Nitric Oxide Production
- Increase IL-1beta, IL-6, IL-15 & IFN-gamma





- Primary Immune Deficiencies
- Intravenous Immunoglobulins (IVIG)
- Subcutaneous route (SCIG)
- Expensive
- Dosage: 0.5 to 2g/kg every 4 weeks
- Side effects: Nausea, Fever, Headaches and Rarely Anaphylaxis





Immune Modulation: Prophylaxis



- Immune modulation (Th2 to Th1 shift)
- Half Therapeutic Dosage
- Safe
- Anti-septic properties
- Anti-inflammatory
- Inhibits the Biofilm





- South African children from poor communities

- Immune system

- Hygiene Theory

- Largest study to date

- Very different results



Lawrie et al, SA Med. J. 2015, 105



The ratio of naïve-to-memory CD4 and CD8 T-cells reaches a 1:1 ratio shortly after the first decade of life in healthy South African children. This is far earlier than in studies from resource-rich countries, where it occurs only during the third or fourth decade of life. We also found increased proportions of natural killer cells and activated T-cells compared to studies from the US and Europe. The dramatic decline in naïve-memory ratio of both T-helper and cytotoxic T-cells and increased activation markers indicate that South African children are exposed to a wider range of environmental pathogens in early life. The marked differences observed in these and other parameters are important in understanding the developing paediatric immune system within an African, poorly resourced context.

Unpublished: Payne H and Nieuwoudt M et al 2015



New Horizons: Immune Cell Potentiating Factor (ICPF)

- Peptides, less than 8KDa long
- Biologic Response Modifier. IL-6 released early. Leads to increased IL-2 expression (growth factor/activator for T-, NK- and B-cells) and IFN-gamma
- Effective Innate Immune Response: Up-regulation of Cytotoxic & Phagocytic Immune Cells, Macrophage Activation, Natural-killer Cell Activation, T-cell Activation & Acute-phase Protein Production
- Sub-cutaneous
- Safe





- Interferon alpha2b
- Large Gap in our understanding
- Revisit Hygiene Hypothesis
- Alternatives to IVIG/SCIG
- Immune Cell Potentiating Factor
- Thank You

