Pros and Cons of IVIG vs SCIG in (South) Africa

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IPOPI 05-10—2012, ESID Florence

Outline

- 1)Brief Ig history
- 2)Uses of Ig in SA
- 3)What is “new” – and best practice for IVIG vs SCIG
- 4)The African Scenario : A.The need for Ig in Africa
- B.The PI profile needing Ig
- C.The availability of Ig
- D. IVIG or SCIG FOR AFRICA ?

1)BRIEF HISTORY OF IG

- WW II : First wide distribution of concentrated purified human immune globulin as albumin preparations for treating shock in battle.
- Human Immune serum globulin (ISG) already in WW II also shown effective in preventing infections with hepatitis, measles and polio

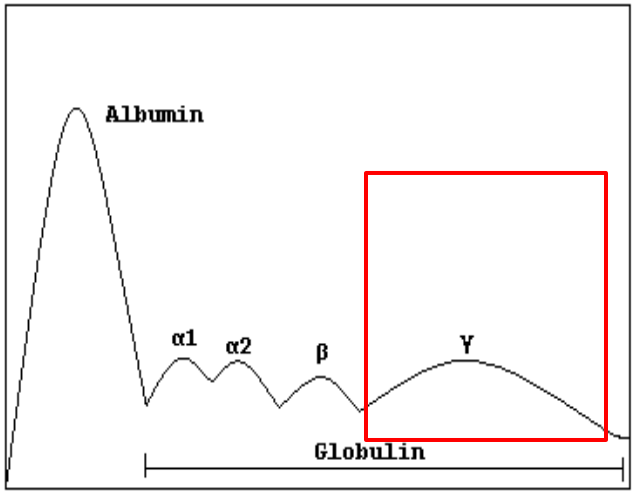
- By late 1940's : Civilian use of ISG in prophylaxis or amelioration of measles and also against specific other infectious diseases for normal but at risk population established.

- **Premature infants receiving ISG injection** – first use in physiologic ID
- AND THEN…..

Melvin Berger, IDF 2008

1952 Bruton OC - SCIG

- 1952 Pediatrics 9:722-728.
- First description of **Ig as replacement therapy in PI Disease**



Bruton provided a relatively crude preparation of immunoglobulin via **the subcutaneous route.** He documented restoration of serum immunoglobulin levels and described a clinical benefit for the patient

Further HISTORY OF IG ….

- Large scale use initially IMI with limited doses and volume, also painful
- Early 1980's, preparations safely given by IVI , first licensed in the U.S. also became available in SA
- 2006 – Re-emergence of SCIG first commercial preparations for subcutaneous immunoglobulin replacement therapy (SCIG) approved by the United States FDA

- The **"survival" of SCIG in Sweden !**

South African Ig History

- 1980's IMI preparation of Ig by local Blood Transfusion Service – unpaid plasma donors and local fractionation, as also Sandoz products in 1980, recently Octopharma reintroduced.
- IMI product (Intragam) used off label for sc use where no other choice for treating Ig deficiency states. SCIG (Beriglobin) available in South Africa marketed for IMI use to date.
- Use of imported plasma curtailed after **tragic infection with HIV** of SA Haemophiliac patients.
- Currently 3 suppliers of IVIG, one supplier supplier registered for SCIG

African Ig History

- South Africa
- Northern Africa –European fractionation with local plasma pool
- Rest of Africa ?

In Africa, up to **902,631** people may have a PID, whereas only **1,016** cases are currently registered.

For Europe, estimate 638,000 cases, and 15,052 cases are currently registered (2.27 %)

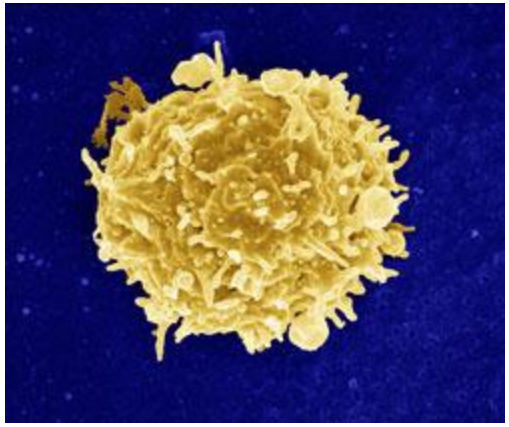
J Clin Immunol. 2012 Jul 31. [Epub ahead of print]**Primary Immunodeficiency Diseases Worldwide: More Common than Generally Thought.Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL, Abel L**

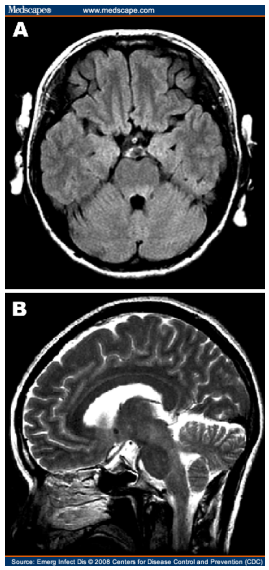
2) Established USES of Ig in PID in South Africa

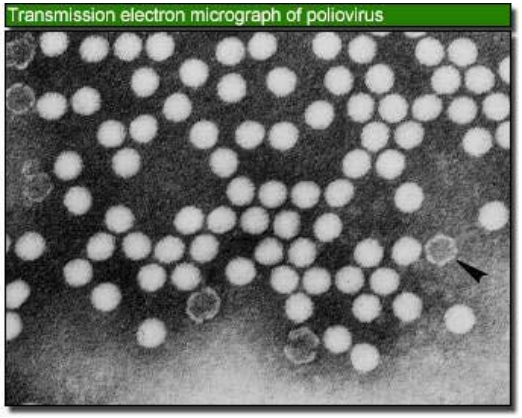
- **Major use of IVIG – not for PI but for neurological conditions**

Case Study: **IViG Keeps Alzheimer's at Bay for a Decade - Yahoo ...news.yahoo.com/case-study-ivig-keeps-alzheimers-bay-decade-2004...18 Jul 2012 – Case Study: IViG Keeps Alzheimer's … Jason Marder watched the inevitable decline of his younger brother, who died of Alzheimer's disease at .**
By STACEY SCHOTT, M.D., and SUSAN DONALDSON JAMES | Good Morning America – Wed, Jul 18, 2012

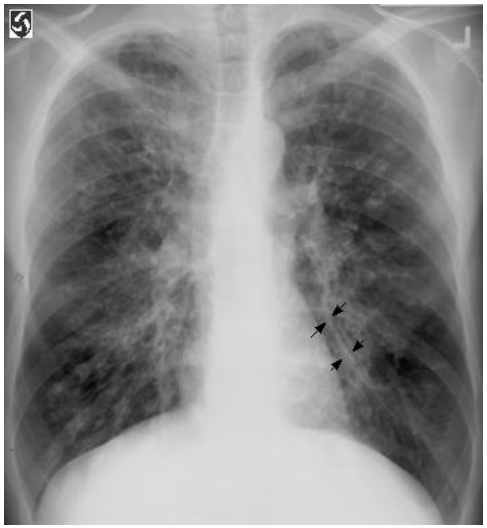
Result of Lack of appropriate therapy in SA : Polio virus complication in Agammaglobulinaemia

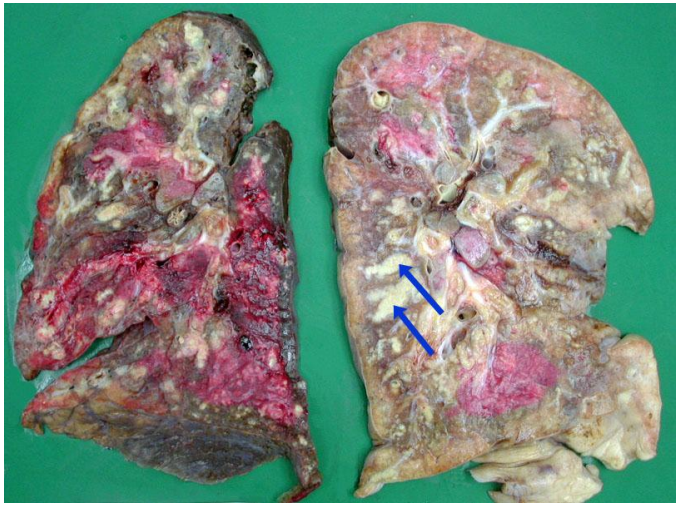


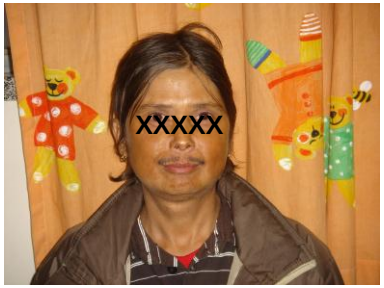




AND : Bronchiectasis :







3) SO WHAT IS NEW ABOUT Ig in SA?

- Increasing demand with - more PID awareness and diagnosis
- Increase in use for other indications – many “off label”
- Increase in production capacity – market forces
- Increased number of products
- Increase in threat of maintained availability - for PI indications

“Best practice” is a constantly moving target –
(J Orange on IVIG)

4) The African Scenario

In Pros and Cons of IVIG and SCIG in SA First considerations :

- Are we applying best practice?
  Lack of national guidelines
- Are we driven by market forces or by evidence based medicine ?
  Lack of marketing control
- Are we practicing in the best interest of the patient and are we cost effective?
  Lack of understanding by Medical insurers and pharmacies AND THEN ONLY
- What is the patient's choice ?

A) The Need for IG in Africa generally

- Relevance of PID varies widely between Northern and Southern Africa
- The availability of Ig varies hugely in Africa

PID in AFRICA

'Orphans' of Africa

Aziz Bousfiha

And ASID Board. June 2011

www.asid.ma

Profile of PID : IUIS 8 Groups

- 1) Combined ID
- 2) Defined Syndromes with ID
- 3) Pred Antibody ID
- 4) Immune Dysregulation ID
- 5) Phagocyte ID
- 6) Innate Immunity ID
- 7) Autoinflammatory disorders ID
- 8) Complement ID

(Frontiers in IMMUNOLOGY NOV 2011,VOL 2,article 54, 1-26)

Over 200 different subtypes with more than 100 gene defects of PID have been identified

B.The PI profile needing Ig

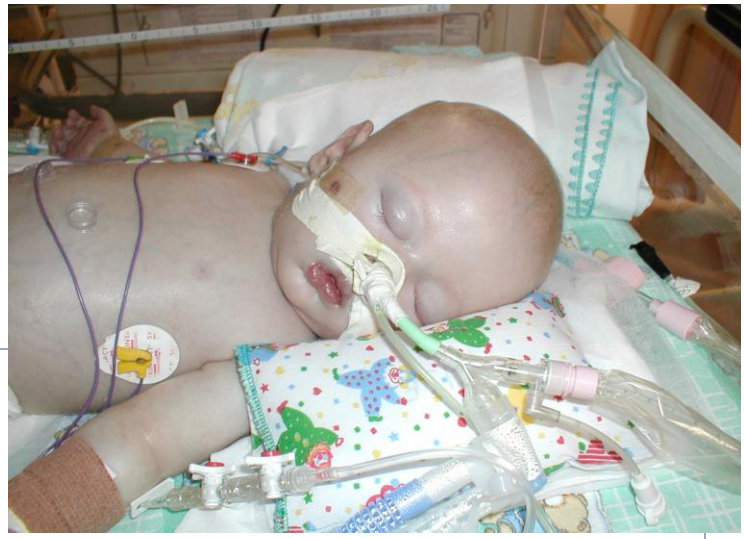
PID Comparison: ASID, ESID & LASID

Variable	ASID[1]	ESID[2]	LASID[3]
Number of reporting countries	5	39	12
Date or period of the analysis	to Oct 2008	2004-2008	1998-2004
Combined T & B cell immunodeficiency	234 (21.5%)	671 (9.03%)	316 (9.5%)
Predominant antibody deficiencies	**331 (30.4%)**	**4073 (54.82%)**	**1764 (53.2%)**
Other well-defined immunodeficiency syndromes	204 (10.7%)	1292 (17.39%)	750 (22.5%)
Diseases of immune dysregulation	15 (0.1%0	98 (1.32%)	11 (0.3%)
Phagocytic disorders	155 (14.2%)	932 (12.54%)	286 (8.6%)
Defects of innate immunity	1 (0.1%)		
Autoinflammatory disorders	10 (1%)	76 (1.02%)	
Complement deficiencies	54 (4.9%)	151 (2.03%)	94 (2.9%)
Unclassified immunodeficiencies		137 (1.84%)	
Total	**1087**	**7430**	**3321**

Frequency of a condition varies between countries also

[1] Bousfiha A, 1st ASID conference, Casablanca, November 2008
[2] Gathmann B, et al. Clin Exp Immunol 2009;157(Suppl 1):3-11
[3] Leiva LE, et al. J Clin Immunol 2007;27:101-108

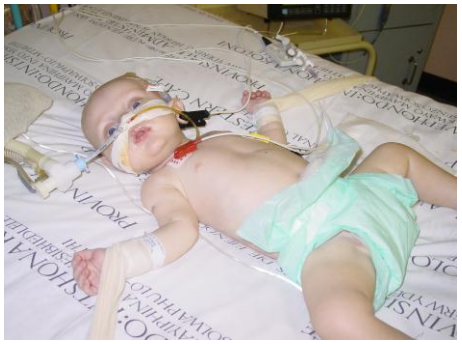
PID in South Africa



SA 49 320 500 Pop
Expected PID 5000

HIV dominates : 5 000 000 (5000 x more)

Tb dominates : Disseminated BCG



Documented risk of disseminated BCG disease in non-HIV-infected infants
is < 5 per 1 million vaccinees and is associated with rare congenital immune deficiencies,
Shown to be 1100 to 4170 per 1 million in HIV-infected infants routinely vaccinated at birth

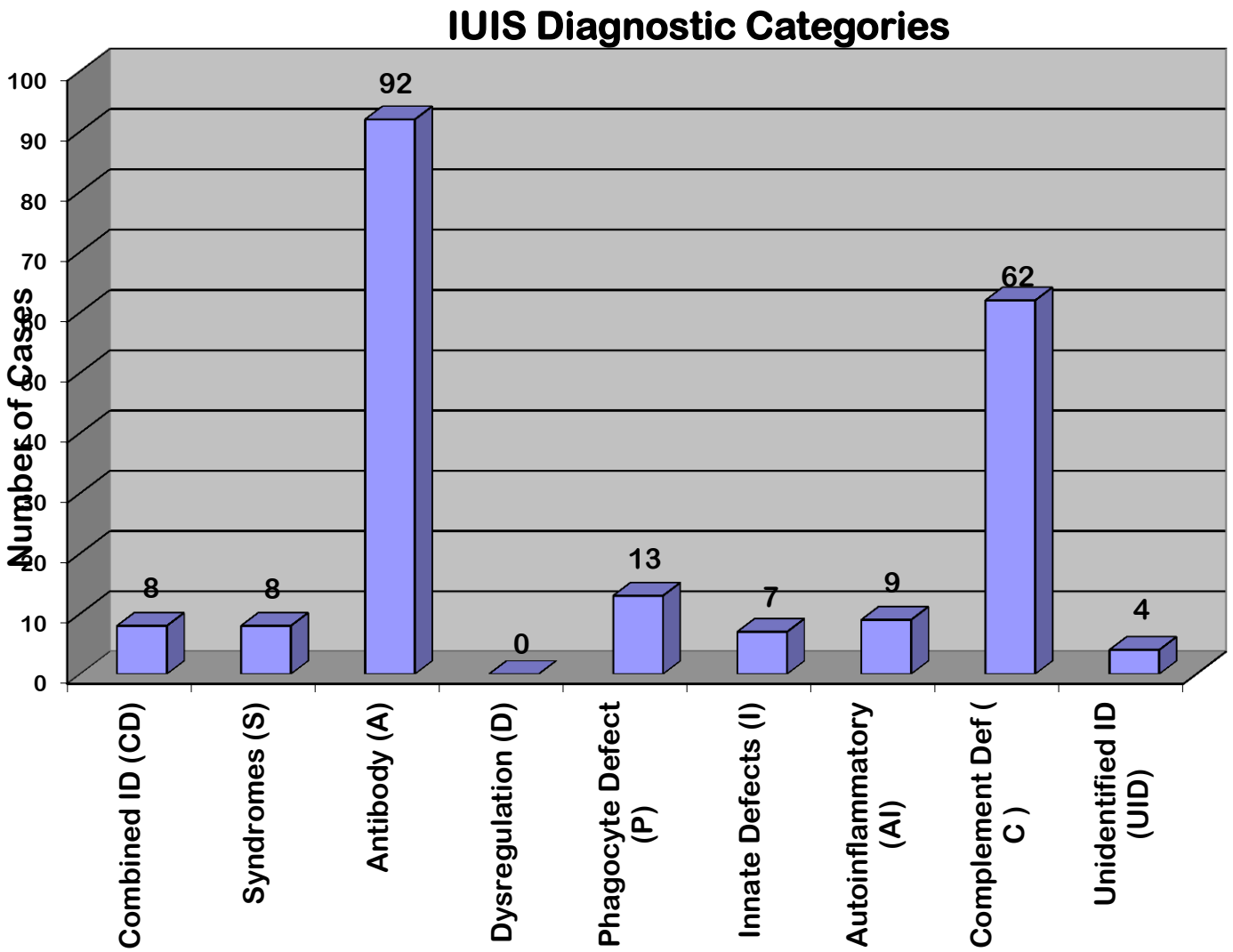
Bulletin of the World Health Organization 2009;87:505-511
Disseminated bacille Calmette–Guérin disease in HIV-infected South African infants.AC Hesseling et al

(Live polio vaccination may also result in dissemination)

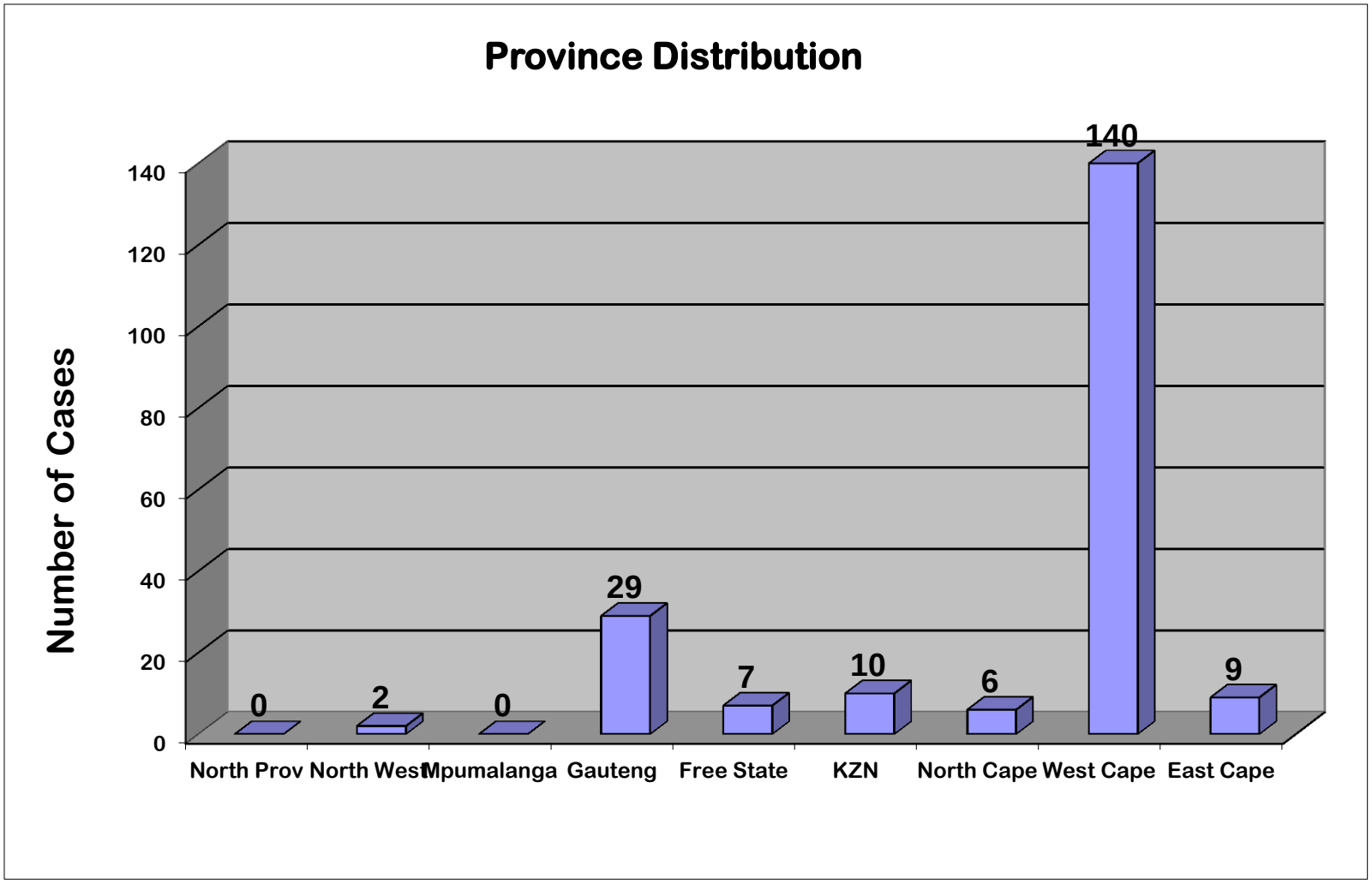
SA DATA

2012 DATA

Categories of 2003 patients



Provinces


Province Distribution
Number of Cases
140
120
100
80
60
40
20
0
0
2
0
29
7
10
6
140
9
North Prov
North West
Mpumalanga
Gauteng
Free State
KZN
North Cape
West Cape
East Cape

- A) The true need for IG in AFRICA ?
- B) The PI profile needing Ig?
- **C) The availability of Ig in Africa ?**
- D) The need for which Ig in Africa ?

Availability of IG is not the first need for PID in Africa-

Comprehensive strategy required:

Diagnosis – Treatment - Monitoring

C) The Availability of Ig in South Africa:

- One fractionation plant – National Bioproducts – IVIG Ploygam and Intragam for IMI. Not registered for SC use. No capacity for remainder of Africa
- Beriglobin – SCIG registered in SA – “abused” IMI
- Pharmaplan – recent re-introduction
- Octagam – new kid on the block

•Remainder of Africa:

- No Fractionation

Ig Reimbursement/Payment in SA

2 Systems, no regulatory authority :

1) State Patient
2) Private Patient

1)Motivation by attending physician with Individual request form for every infusion > 2 grams. Motivation judged by individual Tertiary hospital pharmaceutics review board. Hospital pharmacy budget independent from other patient cost. Only IV for available. Remotivation 6-12/12 or haphazard.
2)Motivation by attending physician as PMB to the respective Medical Aid 6/12, should be fully reimbursed, pending ICD10 code. Rarely SCIG used (currently around 10 patients off label)

ICD 10 codes FOR CLAIMING FROM MEDICAL INSURERS
PMBs include a Chronic Disease List (CDL) published in terms of the Medical Schemes Act , which includes treatment algorithms and the relevant ICD-10 (CDL). Relevant to PIDs are:

D46.0
Refractory anaemia without sideroblasts, so stated
D46.3
Refractory anaemia with excess of blasts with transformation
D46.4
Refractory anaemia, unspecified
D60.0
Chronic acquired pure red cell aplasia
D60.1
Transient acquired pure red cell aplasia
D60.8
Other acquired pure red cell aplasias
D60.9
Acquired pure red cell aplasia, unspecified
D61.0
Constitutional aplastic anaemia
D61.1
Drug-induced aplastic anaemia
D61.2
Aplastic anaemia due to other external agents
D61.3
Idiopathic aplastic anaemia
D61.8
Other specified aplastic anaemias
D61.9
Aplastic anaemia, unspecified
D70
Agranulocytosis
D80.0
Hereditary hypogammaglobulinaemia

D81.0
Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1
Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2
Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.4
Nezelof's syndrome
D81.5
Purine nucleoside phosphorylase [PNP] deficiency
D81.6
Major histocompatibility complex class I deficiency
D81.7
Major histocompatibility complex class II deficiency
D81.8
Other combined immunodeficiencies
D81.9
Combined immunodeficiency, unspecified
D82.0
Wiskott-Aldrich syndrome
D82.1
Di George's syndrome
D82.2
Immunodeficiency with short-limbed stature
D82.3
Immunodeficiency following hereditary defective response to Epstein-Barr virus
D82.4
Hyperimmunoglobulin E [IgE] syndrome
D82.8
Immunodeficiency associated with other specified major defects
D82.9
Immunodeficiency associated with major defect, unspecified

- A) The true need for IG in AFRICA ?
- B) The PI profile needing Ig?
- C) The availability of Ig in Africa ?
- **D) The need for which Ig in Africa ?**

In general

Ig replacement is standard of care for PI

Dose and strategy of administration vary from patient to patient

Aim – prevention of acute and chronic infections, prevention of infectious complications

General dosing guidelines available but individual patient requirements differ to prevent infections rather than achieve a specific trough level.

"**The goal of Ig replacement therapy should be to improve clinical outcome and not to reach a particular IgG trough level**" (Chapel et al)

All forms of administration have to be monitored

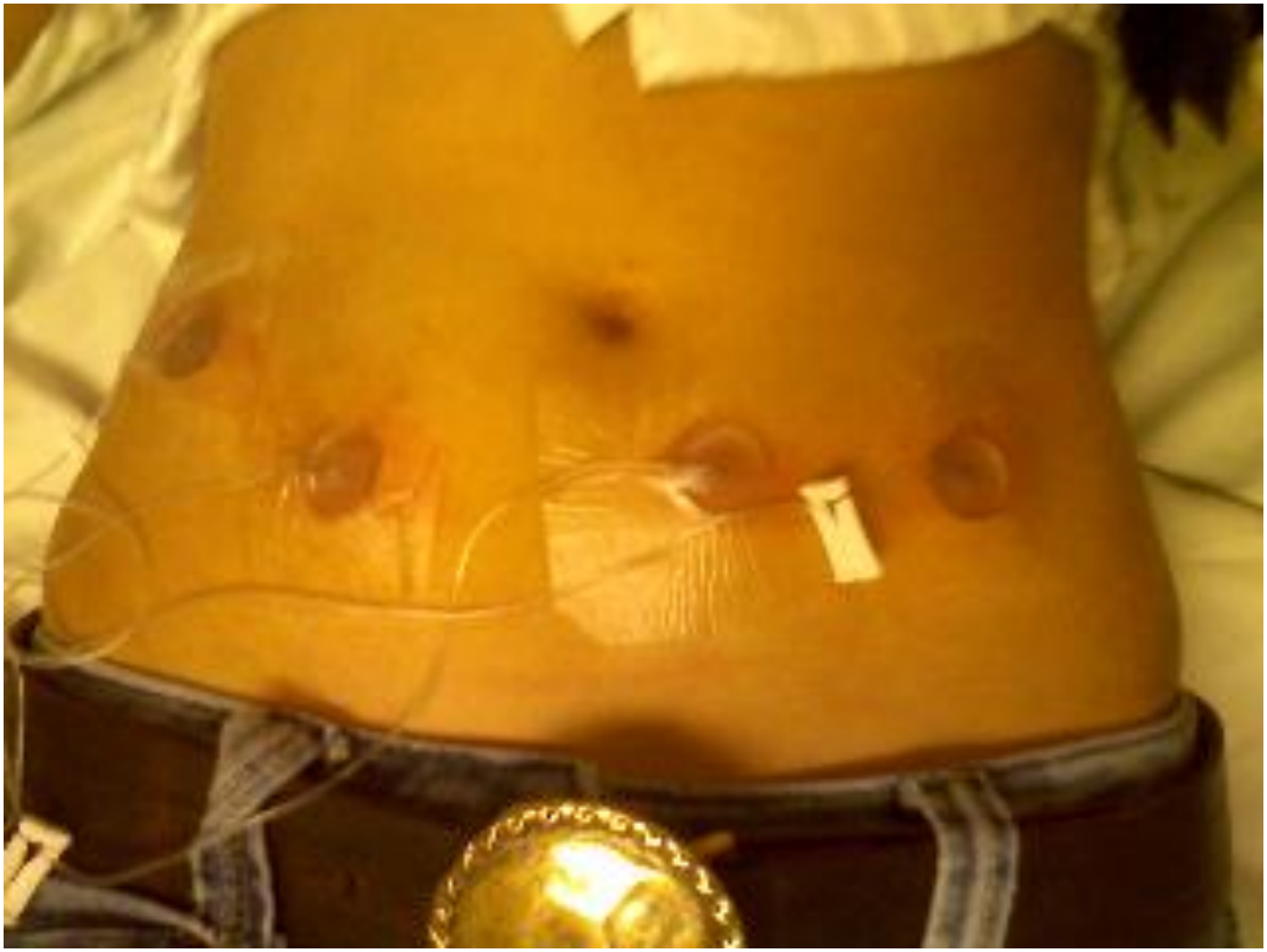
IVIG vs SCIG

Safety & Tolerability - subcutaneous IgG administration remarkably free from systemic adverse events, induction of tolerance to IgA reported when previously sensitive patients were put on subcutaneous IgG

Efficacy- equal both routes

Consistent level of serum IgG important for patients with PI in preventing infections

Subcutaneous Infusion



Major consideration : Side Effects – more severe profile for IVIG

Local : injection-site reaction

Systemic : headache, vomiting, pain, arthralgias, fatigue,fever

Severe : renal dysfunction/failure, thrombotic events, aseptic meningitis syndrome (AMS), hemolysis and transfusion-related acute lung injury

Questions:

- A .The true need for IG in AFRICA ?
- B. The PI profile needing Ig?
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- D. **The need for which Ig in Africa** ?

In AFRICA Summary
Considerations in Selecting Route of IgG Therapy

Clinical Factors

‹ **Ability to establish IV access – VIP**
‹ **Adverse effects** during IV infusions or following peak - **VIP**
‹ Adverse effects/suboptimal health at trough when IV infusion due
‹ History of thromboembolic events
‹ Risk of thrombosis, renal failure, hyperviscosity

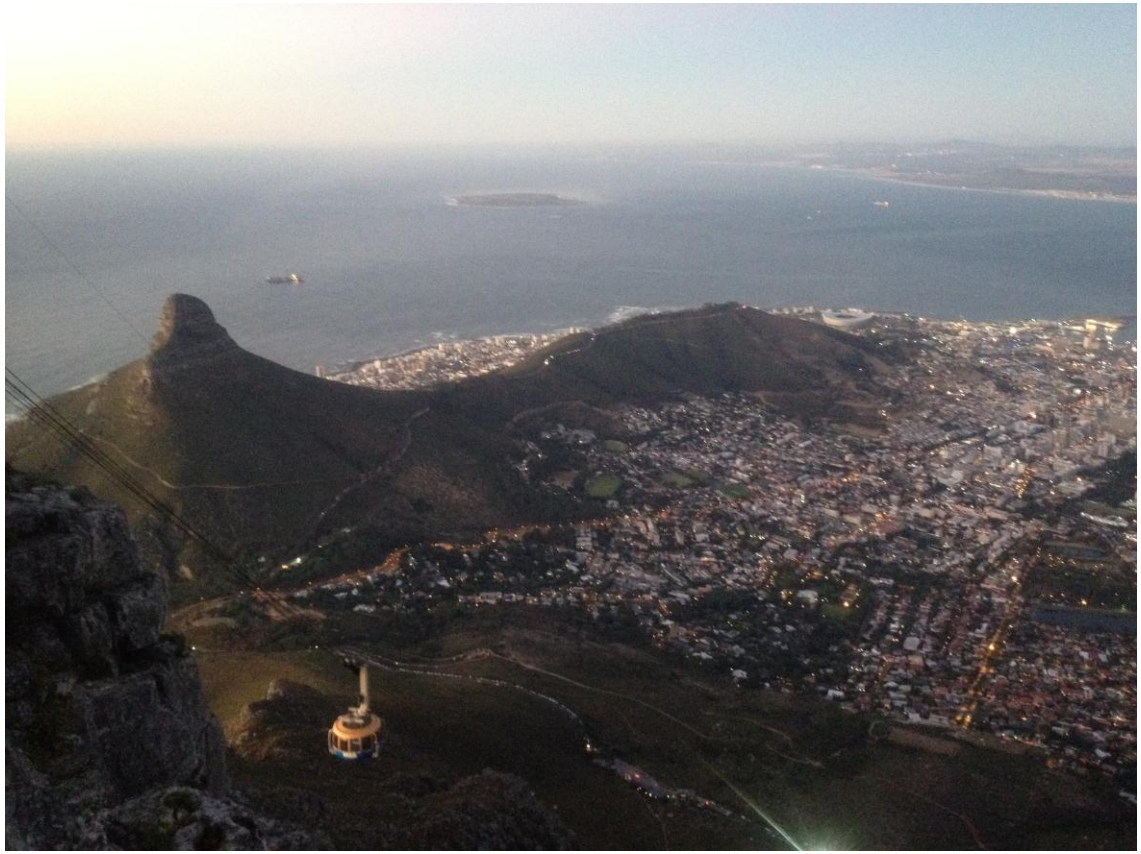
Life Style/Psychological

‹ **Distance from/accessibility of infusion center -VIP**
‹ **Availability of transportation**
‹ Patient's schedule
‹ Availability of home nursing services
‹ Ability to learn and perform infusions
‹ Availability of partner/parent/"infusion buddy"
‹ **Home environment**
‹ **Reliability of patient** (EDUCATION) - **VIP**
‹ **Reimbursement issues** (FUNDING)

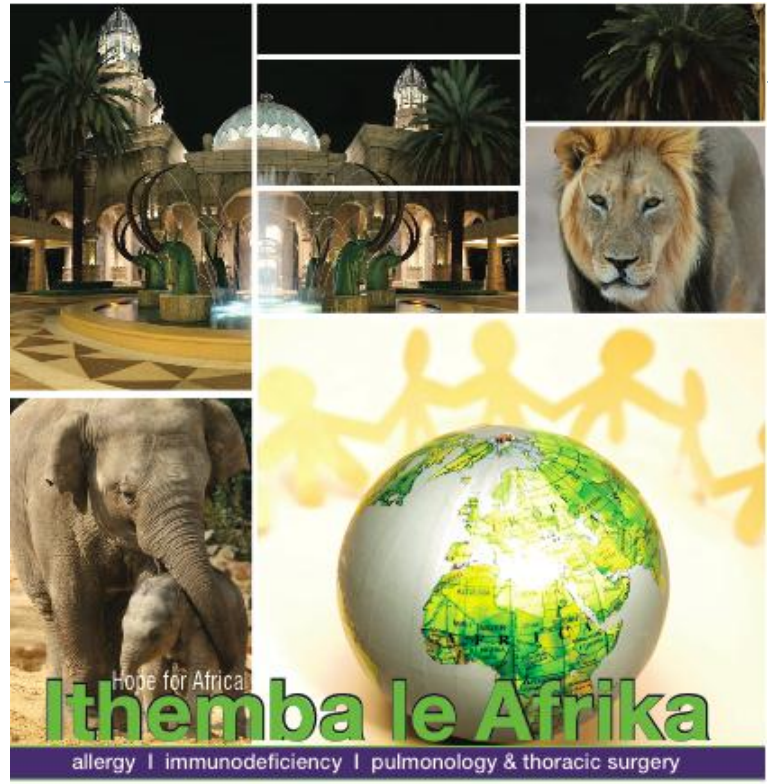
AND EMPOWERMENT

(Courtesy IDF)

Thank You



Welcome to Africa



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