

Intravenous immunoglobulins in  
pediatric practice:  
15 years of experience from North  
India

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## **A clinician should suspect immunodeficiency when a child has**

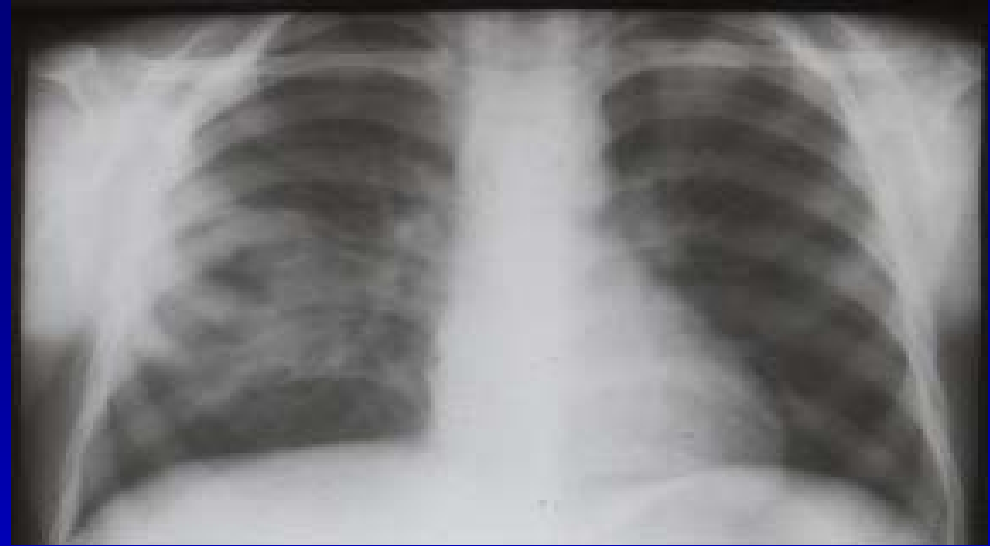
- **Very frequent infections**
- **Very severe infections**
- **An unusual clinical presentation**
- **Infection with an unusual micro-organism**

# **Approach to immunodeficiency**

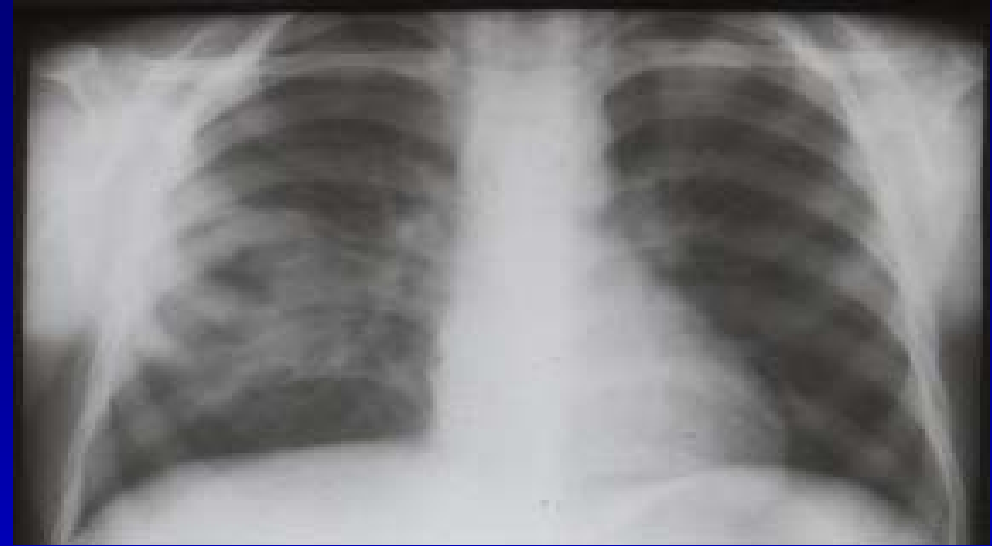
- **Immunodeficiency can be secondary or primary**
- **Infection with HIV is now the commonest cause of secondary immunodeficiency**

# **Approach to immunodeficiency**

- **Diagnosis of PID in the resource poor setting**
- **Very few centres where such a diagnosis can be made**



**4 years old boy**  
**Failure to thrive**  
**Recurrent pneumonia**  
**Arthritis**



**4 years old boy  
Failure to thrive  
Recurrent pneumonia  
Arthritis**

**Bruton's Disease**



**14 months old boy  
Recurrent pneumonia  
Pneumothorax  
Pyoderma**



**Father 31 years  
Ill since early childhood  
Repeated episodes of pneumonia  
Skin abscesses  
Treated for TB  
Treated for drug resistant**



**Son-14 months**



**Father-31 years**

## **Hyper-IgE Syndrome**

# PIDs at Chandigarh: 1992-2005

## Specific

### Cellular

- SCID (7)
- Wiskott - Aldrich syndrome (3)
- DiGeorge syndrome (2)
- Hyper- IgM syndrome (1)

### Humoral

- Bruton's Disease (17)
- CVID (9)
- Tr. Hypo. Infancy (8)
- IgG subclass deficiency (5)
- IgA deficiency (5)
- Ataxia telangiectasia (5)

# PIDs at Chandigarh: 1992-2005

## Non-specific

### Cellular

- Hyper- IgE syndrome (21)
- Chronic granulomatous disease (6)
- Congenital / cyclical neutropenia (2)

### Humoral

- C1- esterase inhibitor deficiency (8)

# **PIDs at Chandigarh: 1992-2005**

## **“Novel” conditions**

- **Chronic mucocutaneous candidiasis (2)**
- **Griscelli syndrome (1)**
- **Papillon Lefevre syndrome (3)**
- **Mycobacteria specific defects: IL-12 receptor deficiency (1)**

# Intravenous immunoglobulins

## Indications:

1. **Bruton's disease**
2. Common variable immunodeficiency
3. IgG subclass deficiency
4. Misc. –  
Wiskott-Aldrich syndrome,  
Hyper-IgM syndrome,  
Transient hypogammaglobulinemia of infancy

# Intravenous immunoglobulins

## Products available:

1. Ivigamma (Bharat Serum and Vaccines Ltd.)
2. Iviglob (VHB Pharmaceuticals)
3. Intraglobin / Pentaglobin (Biotest)
4. Sandoglobulin (Novartis)
5. Misc. – Reliance, Baxter

# Intravenous immunoglobulins

- Cost of product:

<b>Name of product</b>	<b>Approximate cost</b>
Ivigamma / Iviglob	Rs. 2700 per 5 gm.
Intraglobin / Pentaglobin	Rs. 9500 per 5 gm.

# Intravenous immunoglobulins

- Availability

Prior to 1993

1993-1997

After 1997

# Intravenous immunoglobulins

- **Method of administration:**
  1. Usually in hospital / clinic setting
  2. Day care admission
  3. Costs of hospitalization are usually minimal
  4. Subcutaneous administration is not popular

# Who bears the cost ?

- Health insurance is not available to the overwhelming majority
- Reimbursement by government in selected cases
- Provision by the employer?
- Role of non-governmental organizations
- Role of individual donors

# Who bears the cost ?

- How do families cope?
- How does the diagnosis of a PID affect the family dynamics?

# Who bears the cost ?

- Indian Patients Society for Primary Immunodeficiency
- Establishment of a corpus



**Bruton's Disease:  
on regular IVIG therapy**





**Bruton's Disease:  
on regular IVIG therapy**





# IgG Subclasses

- **IgG1** : Antibodies against bacteria (protein ag.)
- **IgG2** : Antibodies against bacteria (polysacch. ag.)
- **IgG3** : Antibodies against viruses (protein ag.)
- **IgG4** : Antibodies against parasites

## Mandatory requirements for IVIG ppns.

- At least 1000 donors in plasma pool
- IgG molecule atleast 90% intact
- Normal IgG subclass proportions
- Minimal IgA concentration
- Proven opsonizing, complement binding and neutralizing activity

## Mandatory requirements for IVIG ppns.

- Free from contaminants eg. PKA
- Modified biochemically as little as possible
- Adequate biological half life
- Safety profile as per current norms

# IVIIGs - Earlier ppns.

## 1<sup>st</sup>. Generation

- Enzyme degraded preparations
  - : proteolytic degradation
    - pepsin, plasmin

## 2<sup>nd</sup>. Generation

- Chemically modified ppns.

# IVIIGs - Currently available ppns.

- Intact molecule
- Complete Fc function
- Normal half-life
- Normal subclass proportions

# IVIIGs - Currently available ppns.

## 3<sup>rd</sup>. Generation

- Intact immunoglobulin

  - : ph4 & pepsin treated

  - : polyethylene glycol treated

# IVIIGs - Currently available ppns.

## 4<sup>th</sup>. generation

- Intact immunoglobulin

- : 99% monomeric IgG

- : low anti-complementary activity

- : 'complete' viral inactivation

- : ready to use liquid formulation

- : storage at room temperature

- : shelf-life 2 years

# IVIIGs - Currently available ppns.

## 4<sup>th</sup>. Generation

- Product: Intratect (Biotest)
  - : made by cation exchange chromatography
  - : three separate processing steps for viral inactivation

## IVIG : Mechanism of action

- Antibodies to cytokines (eg. KD - IL1, IL6)
- Neutralization of superantigens (eg. KD)
- Neutralizing antibodies (eg. against viruses)
- Anti-idiotypic antibodies (eg. ITP)
- Normalization of T-cell numbers and function
- Reduction in expression of adhesion molecules (eg. KD)



# Clinical uses of IVIG

1970s

- First used as substitutive therapy

1980s

- Also started being used for immune-mediated diseases

## As substitutive therapy

- Bruton's Disease
- Common variable immunodeficiency
- IgG subclass deficiency
- After bone marrow transplantation

# For immune mediated diseases

- Kawasaki Disease
- Landry Guillain Barre Syndrome
- Immune thrombocytopenic purpura
- Autoimmune hemolytic anemia
  
- Autoimmune disorders :
  - JDM, SLE, Systemic onset JRA

## Misc. Indications

- Low birth weight babies - prophylaxis / treatment
- Severe bacterial infections
- Myasthenia gravis
- Pediatric HIV infection
- Intractable epilepsy

# Recommended doses

- **Kawasaki Disease:**  
2 gm/kg single dose or 400 mg/kg X 4 days
- **Immune thrombocytopenic purpura:**  
0.5 - 2 gm/kg single dose
- **Hypogammaglobulinemia:**  
0.4 - 0.6 gm/kg every 3 weeks

# Intravenous immunoglobulins

Adverse effects

# Adverse effects of IVIG

## During infusion

- Fever
- Myalgia
- Anaphylactoid / anaphylactic reactions

# Adverse effects of IVIG

## Within 24-48 hours

- Headache, vomiting
- Aseptic meningitis (esp. in children with rheumatic diseases)
- Hyperviscosity syndrome

# Adverse effects of IVIG

## Long term

- All blood products carry inherent risks of transfer of infectious agents
- 'Absolute safety' is an unattainable goal
- Risk, however, may be so low as to be virtually non-existent

## Long term safety of IVIG ppns.

- Enveloped & non-enveloped viruses
- Risk of HCV : the 1983 scare
- Health of the donor
- Donor screening : HCV, HBV, HIV  
: PCR rather than ELISA

# Intravenous immunoglobulins

- Powerful therapeutic tools
- Can be used for immunomodulation as well as for replacement therapy
- Many preparations are available

# Intravenous immunoglobulins

Selection of a product depends upon:

Quality of the preparation

Cost of the preparation

Reputation of the manufacturer

Indication for which it is being used

Safety concerns



# Intramuscular immunoglobulin

- Injections painful
- Doses limited in size & frequency
- Muscle proteases degrade the infused immunoglobulins
- Immunoglobulins reach the circulation after significant delay



# IVIIGs - 1<sup>st</sup>. Generation

- Early sixties; not available now
- Altered IgG molecule – fragments
- Defective Fc function
- Restricted half-life
- Only 40-60% active component retained

# IVIIGs - 2<sup>nd</sup>. Generation

- Molecule is not intact
- Incomplete Fc function
- Lack IgG3 subclass
- Restricted half-life
- Intraglobin / Pentaglobin







- Pediatricians are often called upon to evaluate children for a possible immunodeficiency
- Immunodeficiency can be secondary or primary
- **Infection with HIV is now the commonest cause of secondary immunodeficiency**
- Primary Immunodeficiency Disorders (PIDs) are not being frequently recognized / diagnosed in India

- **Diagnosis of PID is made on the basis of history, physical examination and relevant investigations**
- **Secondary causes of immunodeficiency should be ruled out by appropriate tests**
- **Some disorders can mimic immunodeficiency:**
  - cystic fibrosis,  $\alpha$ -1 antitrypsin deficiency,  
tracheo-esophageal fistula,  
Kartagener's syndrome