A Practical Approach to Combined Immunodeficiencies

Aisha Elmarsafy
Emeritus Professor of Pediatrics
PID Unit – Pediatric Department – Cairo university
ALLSA Congress – 2017
16 September – 2017
Session: Clinical Approaches in PID – Combined Immunodeficiency
Port Elizabeth – South Africa
PID Clinical Presentation

• Not all infections are due to low socioeconomic standard – poor hygiene and malnutrition

• Be aware of: **SPUR**
  • Unusually **S**evere infections
  • **P**ersistent / Complicated infections
  • **U**nusual organisms, infections with low virulence organisms
  • **R**ecurrent infections / **R**uns in the family
IUUS Classification of PID

1. Combined immunodeficiencies
   - Without non-immunologic phenotypes

2. Combined immunodeficiencies with associated or syndromic features

3. Predominantly antibody deficiencies

4. Diseases of immune dysregulation

5. Congenital defects of phagocyte number, function, or both

6. Defects in intrinsic and innate immunity

7. Autoinflammatory disorders

8. Complement deficiencies

9. Phenocopies of PID
SCID/CID

• Heterogeneous group

• Defects of the T cell development and/or T cell function
  • associated to defects of B or NK cells
  • missing T cell help → B cell function is altered even in if normal B cell maturation
Immune effector mechanisms

- Antibody production
- T cell help
- Complement
- Intracellular killing
- Extracellular killing
- PMN
- Cytotoxicity

AAA&I: Primary Immunodeficiency: Genetic & Molecular Mechanisms ppt
Combined immunodeficiency

Antibody production

T cell help

Cytotoxicity

Intracellular killing

Complement

PMN

AAAA&I: Primary Immunodeficiency: Genetic & Molecular Mechanisms ppt
ESID: SCID (severe combined immunodeficiency)

**Definitive**
♂ or ♀ patient < 2 y of age - with either:
   a) maternal T cell engraftment; or
   b) ALC < 3000/mm³ + CD3+ T cells <20%

and at least one of the following:
   1) Mutation in the common γ chain
   2) Mutation in JAK3
   3) Mutation in RAG1 or RAG2
   4) Mutation in IL-7Ra
   5) ADA activity <2% of control ; or mutations in both alleles of ADA

**Probable**
♂ or ♀ patient < 2 y of age with:
   a) maternal T cell engraftment; or
   b) ALC < 3000/mm³ + CD3+ T cells <20%
   c) ↓proliferative responses to mitogens (< 10% of control)
ESID: SCID – Spectrum of disease:

Patients with SCID usually develop

• **Failure to thrive** and **persistent diarrhea**
• **Respiratory symptoms** and/or **oral thrush** in the 1st 2 - 7 m of life
• **Infections:**
  • Pneumocystis pneumonia
  • significant bacterial infections
  • disseminated BCG infection
• **Family history:** consanguinity – previously affected sibs – infant deaths with infections
• Occasionally, no failure to thrive and are not recognized until late in the 1st y of life.

• **SCID is fatal** in the 1st 2 y of life – **unless treated** with:
  • extremely restrictive isolation
  • hematopoietic stem cell transplant or
  • therapy that replaces the abnormal gene / gene product.
CID: additional findings

Hematological abnormalities
- Thrombocytopenia
- Anemias

Specific features
- Ataxia + Telangiectasia
- Neurodevelopmental abnormalities
- Skeletal abnormalities
- Ectodermal dysplasia
Laboratory Evaluation for T cell Defects

- **Absolute lymphocyte count** < 2,500 – 3,000/μL
- **CD3** (< 500/μL); **↓ CD4**; **↓ CD8**
- **↓ Lymphocyte proliferation**
- **Cytokine assays**
- **Molecular studies**
1. **Defective lymphokine signaling:**
   - Defects in the common γ chain
   - JAK3 mutations
   - IL7R-α mutation

2. **Defective cell signaling at and before TCR:**
   - MHC II & MHC I deficiency
   - CD45 deficiency
   - CD3 deficiency

3. **Defective TCR & Ig rearrangement:**
   - RAG1/RAG2 deficiency
   - Artemis
   - DNA-PK

4. **Apoptosis secondary to accumulation of toxic metabolites/ abnormal purine metabolism:**
   - ADA deficiency
   - PNP deficiency

5. **Thymic dysgenensis:**
   - DiGeorge syndrome
   - CHARGE Association

---

The expanding clinical and immunological spectrum of severe combined immunodeficiency

- γc deficiency
- JAK3 deficiency
- IL 7Rα deficiency
- CD 45 deficiency*
- CD 3δ*/CD3ε*/CD3ζ* deficiency
- Coronin-1A deficiency*
- RAG1/RAG2 deficiency
- Artemis deficiency
- DNA-PKcs deficiency*
- ADA deficiency
- Reticular Dysgenesis AK2 def
- Leaky SCID (Omenn S)
- ZAP70

Distribution of SCID based on Genetic Diagnosis

From:
Published online 2015 April 1. doi: 10.1007/s00431-015-2518-4
Mechanism of T-B+ SCID

A: γc/JAK3 signaling pathway
   (adapted from Gaspar et al).

B: T cell receptor with CD3 signaling complex

The expanding clinical and immunological spectrum of severe combined immunodeficiency
SCID with nonfunctional B cells: X-linked (γc) and Jak3

• Receptors for IL-2, 4, 7, 9, 15, 21 share common γ chain (γc)

• Jak 3 is involved in intracellular signaling through γc

• Mutations in common γ chain cause X linked SCID (44%)

• Mutations in Jak 3 cause an autosomal recessive SCID (6%)

• Intracellular signaling through γc and Jak 3 is important in T cell and NK cell development

• Phenotype is T- NK- B+ SCID for both of these forms

Adapted from: R. Buckley, Primary Cellular Immunodeficiencies. JACI May 2002.
SCID with non-functional B cells: IL7R\(\alpha\) Deficiency

• IL7 signaling promotes T cell development and survival through JAK/STAT and PI-3K pathways.

• IL7 signaling is not crucial for B cell or NK cell development in humans (unlike mice).

• Phenotype is T- B+ NK+ SCID

Current Opinion in Immunology 2000, 12:468–473
T-ve  B +ve  NK-ve  SCID
♂ – 3m – no consanguinity
• 1 ♀ (OK)
• 1 ♂: died in NICU – 40d – sepsis
• Since age of 1m: persistent oral thrush + diaper rash

♂ – 5m – no consanguinity
• 1 ♀ (OK)
• 1 ♂: died 3 ½ m – infection?
• Persistent oral thrush + diaper rash
• At 2m: Fever – Diarrhea – Vomiting
• At 4m: Pneumonia
• 4 hospital admissions
<table>
<thead>
<tr>
<th><strong>♂ – 3m – no consanguinity</strong></th>
<th><strong>♂ – 5m – no consanguinity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC: 12,700</td>
<td>TLC: 4,300</td>
</tr>
<tr>
<td>L: 51%</td>
<td>L: 50%</td>
</tr>
<tr>
<td>CD3+: 1.5%</td>
<td>CD3+: 0.3%</td>
</tr>
<tr>
<td>CD3+CD4+: 0.5%</td>
<td>CD3+CD4+: 0%</td>
</tr>
<tr>
<td>CD3+CD8+: 1%</td>
<td>CD3+CD8+: 0.3%</td>
</tr>
<tr>
<td>CD19+ (B cells): 80%</td>
<td>CD19+ (B cells): 92.7%</td>
</tr>
<tr>
<td>CD3-CD56+ (NK cells): 3.3%</td>
<td>CD3-CD56+ (NK cells): 1%</td>
</tr>
<tr>
<td>IgG: 186 mg/dl</td>
<td>IgG: undetectable</td>
</tr>
<tr>
<td>IgM: 18.7 mg/dl</td>
<td>IgM: undetectable</td>
</tr>
<tr>
<td>IgA: &lt; 17.9 mg/dl</td>
<td>IgA: undetectable</td>
</tr>
</tbody>
</table>

**SCID:**

- T-ve
- B+ve
- NK –ve

**? X-SCID**
♂ – 7m – consanguineous parents – 1st sib

• Significant diarrhea soon after birth
• At 5m: Pneumonia – hospitalized – did not resolve
• Persistent oral Thrush & diaper rash
♂ - 7m – consanguineous parents – 1\textsuperscript{st} sib

- TLC: \textbf{4,700}  
  - L: 19\% (\textbf{893})

- CD3+: \textbf{0.3}\%

- CD3+CD4+: \textbf{0}\%

- CD3+CD8+: \textbf{0}\%

- CD19+ (B cells): \textbf{73}\%

- CD3-CD56+ (NK cells): \textbf{11.2}\%

- IgG: \textbf{< 149} mg/dl

- IgM : \textbf{< 9.7} mg/dl

\textbf{SCID}

\textbf{T-ve}

\textbf{B +ve}

\textbf{NK +ve}

(\textit{IL7R-α deficiency})

\textbf{Homo c.482-483 del fs*}
T-ve  B-ve  NK+ve  SCID
SCID: RAG1/2 Deficiency → TCR & BCR recombination defect

- Mutations RAG1 or RAG2 result in arrest of lymphocyte development due to failure of antigen receptor genes rearrangement.

- Autosomal recessive T-B- SCID (3%)

- Omenn Syndrome

AAA&I: Primary Immunodeficiency: Genetic & Molecular Mechanisms ppt
Schematic representation of the 3 steps of the V(D)J recombination process: Mechanism in T-B-SCID

The expanding clinical and immunological spectrum of severe combined immunodeficiency
Died at 5m
Pneumonia
Diarrhea
Hb: 5 g/dl
TLC: 3,700
L: 30% (1,200)

Died at 3m
Pneumonia
Diarrhea
Plat: 51,000
TLC: 4,000
L: 20% (800)

♂ – 3m – consanguineous family
Oral thrush – diaper rash with large buttock ulcers
Pneumonia – Diarrhea
♂ - 3m – consanguineous parents

- TLC: 2,400
- L: 30% (720)
- CD3+: 0.2%
- CD3+CD4+: 0.1%
- CD3+CD8+: 0.1%
- CD19+ (B cells): 4%
- CD3-CD56+ (NK cells): 62%
- IgG: 610 mg/dl
- IgM & IgA: undetectable

SCID

T-ve

B –ve

NK +ve

(RAG1 deficiency)
<table>
<thead>
<tr>
<th>Classical SCID</th>
<th>Omenn Syndrome</th>
<th>Atypical SCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present in infancy</td>
<td>Present in infancy</td>
<td>Present &gt;12 months of age</td>
</tr>
<tr>
<td>Persistent viral respiratory +/− gastrointestinal infection</td>
<td>Erythroderma</td>
<td>Recurrent, severe, prolonged viral infection</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em> pneumonitis</td>
<td>Alopecia</td>
<td>bronchiectasis</td>
</tr>
<tr>
<td>Disseminated BCG infection</td>
<td>Hepatosplenomegaly</td>
<td>Autoimmune cytopenias</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Massive lymphadenopathy</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Superficial candidiasis</td>
<td>Inflammatory pneumonitis/enteritis</td>
<td>Granulomatous cutaneous lesions</td>
</tr>
<tr>
<td>Maternofoetal GFHD</td>
<td>Raised IgE</td>
<td>EBV-associated lymphoproliferation</td>
</tr>
<tr>
<td>Absent lymphoid tissue</td>
<td>Eosinophilia</td>
<td>Partial or restricted antigen-specific antibody responses</td>
</tr>
<tr>
<td>Absent immunoglobulins Absent T lymphocytes</td>
<td>Lymphocytosis</td>
<td>Lymphopenia</td>
</tr>
</tbody>
</table>
Omenn Syndrome
♂ – 4m – consanguineous parents – 1st sib

- Dermatitis: erythroderma – scaly – exfoliative – very itchy
- Alopecia
- Diarrhea (persistent) – edema
- Failure to thrive – wt: 3.400 Kg
- Pneumonia – pericardial effusion (suppurative)
- Blood transfusion: exacerbation of manifestations
- Hepatosplenomegaly – LN enlargement
♂ – 4m – consanguineous parents – 1st sib

- Hb: **5.4 g/dl**
- TLC: **38,500 - 21,300 - 38,000**
- L: 10% (3,850) - 58% - 10% (3,800)
- CD3: **90%**
- CD4: **20%**
- CD8: **70%**
- CD19: **0%**
- CD56: **2.8%**
- IgG: **<149**
- IgM: **<23**
- IgA: **<17.9**
Homozygous deletion in RAG1

c.1277_1279delAAG
p.E425del

aa alignment:

KLQVKAFADK-EGDVKS
KLQVKAFADKEEGDVKS

Patient

Normal sequence
Atypical SCID
P-CID
♀ – 4y old – non-consanguineous parents

- At 2 wk: **exfoliative skin rash** – topical steroids
- At 3m: **keratitis** - corneal opacity – antibiotics + corneal transplant
- Since age of 1y:
  - Repeated **pneumonias** – recurrent **draining ears**
  - **Unresolving diarrhea** – stools: +ve *Cryptosporidium*
  - **Hepatopathy**: steatosis and mild portal fibrosis – dilated bile ducts
- Since age of 2y: **repeated hemolytic episodes** (every 3 wks) –
  - Coomb’s +ve – difficult to match – responds to corticosteroids
- **Bronchiectasis**: *Pseudomonas*
♀ – 4y old – non-consanguineous parents (seen on 10/2016)

• Hb: 4 – 7 g/dl
• No leucopenia: 7,000 – 12,000
• No lymphopenia: 3,000 – 4,000
• CF: -ve    HIV: -ve

• CD3+: 60% (1155)
• CD3+CD4+: 2.2% (42)
• CD19+: 4.5% (86)
• IgG: 3,000 mg/dl    IgM: 330 mg/dl
• IgA: <17.9 mg/dl    IgE: 8.5 IU/ml
• HLA-DR: normal
• DHR test: normal
♀ – 4y old – non-consanguineous parents (seen on 10/2016)

Sanger sequencing for RAG1/RAG2

• RAG1 compound heterozygous mutation:
  • c.1003T>C p.C335R [mother: heterozygous]

• c.2434C>T p.Q812* [father: heterozygous]
  (our group previously reported it in an Egyptian with Omenn syndrome – 2015 - novel mutation)
♀ – 4y old – consanguineous parents

- **2 ♂ died (6m – 13m):**
  - diarrhea – pneumonia
  - small heads – delayed developmental milestones
- At 6m: prolonged **diarrhea**
- At 8m: **Pneumonia** – oral thrush
- At 10m: **microcephaly** – **hypotonia** – delayed motor development
- Repeated **pneumonias**
- Frequent **autoimmune hemolytic anemia** – **Coomb’s +ve** – difficult to match
  - Corticosteroids – cyclosporine – azathioprine – IVIG - transfusions
♀ – 4y old – consanguineous parents

- Hb: 4 - 5.6 Coomb’s +ve
- Eosinophils: 16-24%
- HIV: -ve
- EBV, CMV, HCV: +ve
- Corona Virus OC 43,
- Para influenza virus type 4,
- Boca virus: +ve
- Sputum: Klebsiella & Candida

- TLC: 3,000 ALC: 1,300
- CD3+: 38% (500)
- CD4+: 14% (185)
- CD19+: 15% (190)
- CD4+ CD45RA+: 6%
- IgG: >2,800 IgM: 370
- IgA: 88 IgE: 6.2
♀ – 4y old – consanguineous parents

WES
homozygous mutation in the gene encoding PNP
(c.172 C>T ; p.Arg58*)

• Serum Uric acid: low - 1.10 mg/dl (2 – 5.5 mg/dl)
  • Confirmed by enzyme assay
• Fully matched with her sister but we lost her while being prepared for HSCT
Biochemical Pathway of Purine Metabolism

Ribose-5-phosphate

PP riboseP

GMP (deoxy)guanosine

HGPRT (deoxy)inosine

IMP

AMP

AMP (deoxy)adenosine

ADA

APRT

adenine

guanine

hypoxanthine

xanthine

uric acid

NP
Delay between 1st symptoms to diagnosis for atypical and typical SCID patients

Delay between diagnosis to treatment for atypical and typical SCID patients

Wiskot Aldrich Syndrome (WAS)
♂ – 10m – no consanguinity

- Circumcision - transfusions
- Purpuric eruptions
- Melena
- Persistent Fever
- Marked Pallor
- Splenomegaly
- Failure to thrive
- Wt: 5.9 kg
- Skin rash – Itchy Eczema
- Blood & Platelet transfusions
♂ – 10m – no consanguinity – 1st sib

- Hb: **5.8** g/dl
- Plat: **10,000 – 50,000**/ mm³
- MPV: 6
- TLC: 10,000 - 22,000
- L: 50% (5,000)
- E: 22%

- CD3: 70%
- CD4: 17%
- CD8: 30%
- CD19: 6.4%
- CD56: 6%

- IgG: 1,800
- IgM: zero
- IgA: 166 mg/dl
Confirmation of Diagnosis

• The WIP/WASP FACS or WB:
  • Normal WIP
  • No WASP

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WASP</td>
<td>1.5% (67%)</td>
</tr>
<tr>
<td>CD3+WASP</td>
<td>0.8% (78%)</td>
</tr>
<tr>
<td>CD19+WASP</td>
<td>1% (85.3%)</td>
</tr>
<tr>
<td>CD56+WASP</td>
<td>0% (84.7%)</td>
</tr>
</tbody>
</table>

• Sanger sequencing:
  • a pathogenic mutation in WAS gene as follows:
    • G.48543975_48543976insT
    • C.347_348insT
    • P. V105CfsX15
DiGeorge Syndrome
♀- 9m consanguineous parents – 1st sib

- At 15d: recognized to suffer a complex congenital heart defect
  - Sent to Italy for repair
  - Ca /Pi/Parathormone: were normal

- Chromosomal analysis:
  - FISH for 22: del(22)(q11.2q11.2)(TUPLE1-),22qter(N85A3x2)
  - Microdeletion of the region DiGeorge/VCFS

- TLC: 7,900      ALC: 30% (2,370)
- CD3: 21%       CD4: 8.2%       CD8: 11.2%
- CD4+ CD31+ CD45RA+: 1.7%
DiGeorge Syndrome

- **Microdeletion:** 22q11.2 (DGS critical region)
- **Characteristic facies:**
  - Retrognathia or micrognathia
  - Hypertolerism
  - High and broad nasal bridge
  - Downturned mouth (fish-mouth)
  - Short philtrum
  - Low-set, malformed ears
- **Congenital heart defects**
- **Cleft palate**
- **Thymic hypoplasia:** Immune deficiencies
- **Hypoparathyroidism:** ↓ Ca – ↑ Pi – ↓ parathormone
- **Diagnosis:** FISH – mutational identification
Ataxia Telangiectasia (AT)
♂ - 7y – consanguineous
2 ♀ died (3 – 6y): Pneumonias

• Since the age of 2m: developed > 10 pneumonias
• Persistent chesty (considered asthma) – bilateral draining ears
• CT chest:
  • Rt upper lobar segmental consolidation with cavity formation
  • small areas of atelectasis - mild pleural effusion
  • multiple retrocaval, prevascular, pretracheal LNs
• At 4y: noticed to suffer progressive ataxia
  • clumsiness, falling of objects and abnormal gait
• CT Brain:
  • Mild hypoplasia of cerebellar vermis, mild cerebellar volume loss with prominent folia
• Wt: 9 kg          Ht: 99 cm       (FTT)
♂ - 7y – consanguineous
2 ♀ died (3 – 6y): Pneumonias

- Hb: 8.5
- TLC: 14,000
- L: 30%
- α-feto protein: 1220 ng/ml (<10)
- CD3: 70%
- CD4: 30%
- CD8: 40%
- IgG: 228 mg/dl
- IgM: 374 mg/dl
- IgA: 0
DOCK 8 deficiency (AR-HIES)
♀ – 9y – consanguineous parents

- 3 similarly affected sibs:
  - 2 died (♀ 6y – ♂ 4 ½ y) + 1 ♀(4 ½ y - affected – living)
- Newborn rash
- At 4 m: Recurrent wheezy chest
- At 7 m: Fever – axillary abscesses
- At 18 m: Chronic draining ears – severe cutaneous herpetic rash (peri-oral; peri-umbilical)
- At 3y: Pneumonia
- Diffuse extensive eczema - lichenified fissured skin
- Oral candidiasis - Inter digital candidal infection - Severe groin area infection
- Sclerosing cholangitis: Cryptosporidium
• Eosinophilia (26%)
• Serum IgE: 17,000 IU/mL
• CD4: 10% (265)
• No DOCK8 ptn expression (FACS)
• V low CD19+ IgD- CD27+ (↓B memory)

♀ – 9y – consanguineous parents
14/09/2014

21/09/2014
Topical antifungal
Systemic antibiotics
Systemic antihistamine
<table>
<thead>
<tr>
<th>cons</th>
<th>Sib affect</th>
<th>Other clin</th>
<th>TLC</th>
<th>ALC</th>
<th>Other lab</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD19</th>
<th>CD56</th>
<th>Igs</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-SCID</td>
<td>-</td>
<td>♂</td>
<td>-</td>
<td>↓</td>
<td>↓↓</td>
<td>-</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>JAK3</td>
<td>+</td>
<td>♂ ♀</td>
<td>-</td>
<td>↓</td>
<td>↓↓</td>
<td>-</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>IL7-Rα</td>
<td>+</td>
<td>♂ ♀</td>
<td>-</td>
<td>↓</td>
<td>↓↓</td>
<td>-</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑</td>
<td>N/↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>RAG1/RAG2</td>
<td>+</td>
<td>♂ ♀</td>
<td>Rash?</td>
<td>↓</td>
<td>↓↓</td>
<td>-</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N/↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Artemis</td>
<td>+</td>
<td>♂ ♀</td>
<td>-</td>
<td>↓</td>
<td>↓↓</td>
<td>-</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N/↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>DNA ligase</td>
<td>+</td>
<td>♂ ♀</td>
<td>somatic</td>
<td>↓</td>
<td>↓↓</td>
<td>-</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N/↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>ADA</td>
<td>+</td>
<td>♂ ♀</td>
<td>skeletal</td>
<td>↓</td>
<td>↓↓</td>
<td>cytopenias</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>PNP</td>
<td>+</td>
<td>♂ ♀</td>
<td>neurological</td>
<td>↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
<td>N/↑</td>
<td>N</td>
</tr>
<tr>
<td>Omenn</td>
<td>+</td>
<td>♂ ♀</td>
<td>Rash – alopecia – HSM - erythroderma</td>
<td>↓</td>
<td>N Or ↑</td>
<td>↓</td>
<td>N Or ↑</td>
<td>Esinophilia ↑IgE cytopenias</td>
<td>?</td>
<td>↓↓</td>
<td>?</td>
</tr>
</tbody>
</table>
SCID is a pediatric emergency

The speed of action from clinical suspicion to a diagnosis is crucial - no time for waiting.

Early diagnosis offers better prognosis and outcome of BMT.

Analysis of Molecular Basis of PID:

• Contributes to better understanding of the immune system development/physiology

• Allows:
  • Precise molecular diagnosis
  • Genetic counseling – Prenatal diagnosis
  • Innovative therapeutic approaches (gene therapy)
Management of Combined Immunodeficiency

- Avoid live attenuated vaccines
- Avoid fresh blood transfusion (irradiated)
- Antimicrobials
  - TMP/SMX prophylaxis
  - Antifungal
  - Antiviral
  - Anti tuberculous
  - Antibiotics
- IVIG
- BMT
- Gene Therapy?
Thank you