Primary Immunodeficiencies

• Over 150 heritable disorders of immunity are known; more discovered each year.
• They are individually very rare; precise incidence not known.
• Certain populations have high incidence due to a founder effect.
• All confer increased rate of infections, but infections are common in pediatrics.
• High index of suspicion is needed.

Immune Defects and Infections

Innate Immune Defects
• NK cell--virus-infected cells, cancer cells
• Granulocyte--staph, other bacteria
• Macrophage activation--mycobacteria, salmonella
• Late complement components (C5-9)--neisseria

Adaptive Immune Defects
• T cell or combined--viruses, fungi and bacteria; opportunistic pathogens
• B cell--bacteria, respiratory and GI infections
History and Physical Exam in Primary Immune Diseases

- Infections
  - Frequent
  - Severe
  - Recurrent
  - Persistent, despite standard therapy
  - Caused by opportunistic pathogens
- Failure to thrive in children
- Dysregulated immune reactions
  - Autoimmunity
- Family history

Term baby; went home at 2 days

Now 4 weeks old with omphalitis, delayed umbilical cord separation. No pus.

Leukocyte Adhesion Disorder (LAD)

*High WBC, neutrophils; gingivitis.*

If Immunodeficiency Possible...

GIVE ONLY killed vaccines.
- Do not give live rotavirus, varicella, MMR;
- Use killed influenza, not intranasal;
  - *live polio vaccine has been replaced for infants by killed vaccine in the USA*

Transfuse ONLY irradiated blood products that are negative for cytomegalovirus (CMV)
**Laboratory Tests to Screen for Immunodeficiency**

- CBC and diff—Compare to age-appropriate norms
  - Low absolute lymphocytes (< 2,500 in newborn) may mean SCID
- Number and appearance of granulocytes
- Basic adaptive immune system studies
  - Rule out HIV
  - Total and specific antibodies (IgG crosses placenta after 34 wk)
- Use a sequential approach, guided by clinical and lab findings
  - Lymphocyte tests: Cell surface markers by flow cytometry
    - Proliferation to mitogens (PHA) and antigens (candida)
    - Delayed-type skin hypersensitivity tests (not under 2 y)
  - Antibodies: Concentrations: IgG, IgM, IgA, IgE
  - Specific antibody production: antibody titers to immunization antigens (tetanus, pneumococcus; isohemagglutinins
  - IgG subclasses
  - Granulocyte oxidative burst for Chronic Granulomatous Disease
  - CD18 expression for LAD

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**Supportive Treatment**

- IgG replacement from pooled normal donors, IVIG
- Antibiotics for prophylaxis against
  - Bacteria (Staph, respiratory pathogens)
  - Viruses (Herpes, varicella)
  - Fungi (Pneumocystis)
- Isolation to avoid infectious exposures

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**Definitive Treatment**

- Specific replacement of a missing gene product: PEG-ADA for ADA deficient SCID
- Hematopoietic stem cell transplantation
- Gene therapy, still experimental (for ADA deficiency, X-linked SCID)
Severe varicella after chickenpox vaccine. Pneumonia and hemorrhagic blisters.
T cell deficiency. “Leaky” or partial SCID.
Low T cell numbers, poor proliferation in vitro.

Severe Combined Immunodeficiency (SCID)
• Profound lack of T-cell and B-cell immunity
• Excessive, recurrent, and opportunistic infections from 2-4 months
• Fatal in infancy without immune reconstitution

X-Linked Inheritance of SCID
8 month old baby girl healthy at birth

Developed diarrhea after 2nd rotavirus vaccine at 4 mo. Diarrhea, stopped gaining weight. Then got periorbital cellulitis.


Lymphocyte count of 1410; age normal >2,500.

Stool: rotavirus; found by sequence analysis to be vaccine strain.

Most Often SCID Is Sporadic

19 Genes for SCID in 2010

Genes

Justifications for Newborn Screening

<table>
<thead>
<tr>
<th>Proposed Screening Criteria</th>
<th>How SCID Meets Criteria</th>
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<tr>
<td>Disease is serious</td>
<td>Fatal in first year of life if untreated</td>
</tr>
<tr>
<td>Disease is not detected by exam</td>
<td>Newborns with SCID appear healthy</td>
</tr>
<tr>
<td>Incidence supports screening</td>
<td>Incidence unknown, estimate 1/100,000</td>
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<tr>
<td>Confirmative testing is well-established</td>
<td>T cell counts, mitogen responses</td>
</tr>
<tr>
<td>Effective treatment exists</td>
<td>Bone marrow transplantation (BMT)</td>
</tr>
<tr>
<td>Earlier treatment is better</td>
<td>Best survival and outcome when treated before infections set in</td>
</tr>
<tr>
<td>Diagnosis and treatment are available</td>
<td>Pediatric immunology BMT centers</td>
</tr>
<tr>
<td>Screening is cost-effective</td>
<td>An inexpensive, high-throughout screening test could save many lives</td>
</tr>
</tbody>
</table>
Incidence of SCID--?

- 19 new U.S. infants with IL2RG mutations in Puck lab at NHGRI in 1 year (2002).
- 4,000,000 U.S. births/year; 47% of SCID is IL2RG.
- If 100% of the 2002 cases were identified and sent to Puck lab at NIH for mutation testing, IL2RG SCID incidence would be 1/210,000 births.
- Minimal incidence for IL2RG plus other types of SCID = 1/100,000, comparable to biotinidase deficiency, galactosemia.
- Diagnosis related to family resources, sometimes made only on autopsy.

SCID Patients Treated with BMT Early Have Better Survival

Duke BMT older vs. younger than 3.5 months (R. Buckley)

How to Screen for SCID in Newborns?

- Low lymphocyte counts (in most cases).
- Maternal T cells, patient B cells can be present.
- All SCID patients fail to make normal T cells.

Kalman et al., Genet Med 6:16, 2004
New T cells come from the thymus
• Thymus produces new T cells with antigen specificity determined by T cell receptor gene DNA recombination.
• Excised segments of DNA form circles (TRECs) as a byproduct
• TRECs are stable and can be detected by PCR in newly formed T cells
• TRECs are diluted out as T cells undergo many divisions in the periphery
• Newborns have the most TRECs; TRECs decrease as thymus involutes in adults

### Generation of T Cell Receptor Excision Circles -- TRECs

![Diagram of TCR AV to AJ recombination](image)

70% of αβ T cells make this

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### TREC Assay Procedure

1. Guthrie Card
2. 50 ul blood
3. 3 ul, 1/8" punch
4. DNA Extraction
5. Quantitation of TRECs by Real-time PCR

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### SCID Actual Guthrie Card

![Graph showing copy number per punch](image)
17 Atchekan SCID Patients with BMT at UCSF  

Mort Cowan

ARTEMIS (DCLRE1C) is a DNA repair protein 1/2000 Navajo births homozygous for Y192X

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Navajo SCID Newborn Screening Study  

J Puck, D Hu

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Conclusions

1. SCID is caused by defects in non-redundant gene products required for lymphocyte development. SCID infants appear normal at birth and most cases are sporadic.
2. SCID diagnosed early is treatable, even curable; but SCID is fatal if not treated.
3. Newborns can be screened for SCID with a TREC assay.
4. Identifying infants by screening for low TRECs will
   - Avoid harm from live vaccine with rotavirus, an otherwise beneficial public health measure.
   - Improve SCID patient outcomes.
   - Establish incidence of SCID and other T-lymphocytopenias.
   - Identify of further SCID defects.
Summary

1. High index of suspicion needed to diagnose rare immune defects.
2. Stepwise immune workup for frequent, severe or unusual infections or failure to thrive. Start with CBC/diff, quantitative Ig's; use age-appropriate normal values for comparison.
3. Avoid live vaccines if considering immune deficiency.
4. Give prophylactic antibiotics & IVIG; give only irradiated, CMV negative blood products.
5. Refer to immunology centers for specialized workup and treatment; PIDTC reflects centers of excellence.
6. Newborn screening for SCID could avoid infections and allow early treatment. On May 21, 2010, DHHS Secretary Sibelius endorsed addition of SCID screening to newborn the national uniform screening panel.

References