TESTING FOR PRIMARY IMMUNODEFICIENCY ON THE NEWBORN SCREEN

Dr. Rebecca Scherzer
Goals and Objectives

• Overview of the Immune System
• Review the Criteria for consideration of putting a test on the Newborn Screen
• Discuss Severe Combined Immunodeficiency and testing for that disease of the Newborn Screen
Why is the immune system so important?
Immune System

Two interrelated activities

- **Recognition**: The immune system is able to differentiate between self and nonself. It is able to recognize even subtle differences between foreign organisms.

- **Response**: Once a foreign organism is recognized the immune system enlists a variety of cells and molecules to mount an appropriate response.
Immune System

- **Innate Immunity**: the basic resistance to disease that one is born with

- **Adaptive Immunity**: requires a functioning immune system using lymphocytes and their products
Innate Immune System

- Response in the first 12 hours after exposure to pathogen or tumor cell
  - Epithelial cells
  - Complement
  - TLR (toll-like receptor)
  - Phagocytic cells
  - NK Cells
Adaptive Immune System

- Stimulation from Innate Immune system leads to a more pathogen specific response—Adaptive Immunity
  - Process starts around 24 hours after exposure
  - Cells are activated » Proliferation » Maturation in effector cells
Acquired Immunity

- Antigenic Specificity
  - can distinguish subtle differences among antigens

- Diversity
  - can generate tremendous diversity in its recognition molecules—can specifically recognize billions of unique structures on foreign antigens
Acquired Immunity

 Immunologic Memory
  ▪ Repeated encounters with the same antigen leads to a greater immune reaction- can confer life-long immunity to various infectious agents

 Recognition of Self vs. Non-self
  ▪ Immune system only responds to non-self antigens
Cells of the Adaptive Immune System

- **T-Cells**
  - Mature and become effector cells
    - Killer cells or regulatory cells

- **B-Cells**
  - When mature become
    - Plasma cells » secrete immunoglobulin
    - Memory Cells » cells that are retained and allow rapid response with subsequent encounter with pathogen
The Important Parts

Skin—Barrier to the outside world

T CELLS

B CELLS

PHAGOCYTES

LYMPHOCYTES

IMMUNOGLOBULIN

COMPLEMENT
Severe Combined Immune Deficiency (SCID)

- **Definition:** A rare syndrome due to a variety of genetic abnormalities resulting in a profound deficiency of lymphocytes.
- “Bubble Boy Disease”
- Deficiency of both T and B cell,
- +/- Natural Killer cell function.
- Pediatric emergency
# Severe Combined Immunodeficiency (SCID)

<table>
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<tr>
<th>Condition</th>
<th>T-cell and B-cell Defects</th>
<th>NK Cells</th>
<th>B Cells</th>
<th>Genomic Location</th>
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<td>Omenn’s Syndrome</td>
<td>Variable</td>
<td></td>
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SCID

- Frequent Clinical Presentations:
  - Symptoms usually start in the first 6 months of life
  - FTT
  - Recurrent Infections
  - Recurrent/Persistent diarrhea (often no specific cause)
  - Recurrent/recalcitrant thrush
  - Chronic/Severe respiratory infections
  - Skin rash/erythroderma
SCID: Clinical Presentation

- *Pneumocystis pneumonia* (PJP) [think T cell defect!]
- Severe varicella
- Mycobacterial infection from BCG
- Rash -- Graft versus host disease -- may present prior to transplant due to reaction of maternal T cells
SCID: Diagnosis

- Need to 1\textsuperscript{st} have a high level of suspicion

- Screen with CBC with differential
  
  -- Calculate ABSOLUTE LYMPHOCYTE COUNT (ALC)
  
  Total WBC \times \text{percentage of lymphocytes} = \text{ALC}
# How to Calculate the ALC

WBC  Latest Range: 18.1

**DIFF TYPE**

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<th>Type</th>
<th>Value</th>
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<td>MONOCYTE</td>
<td>6</td>
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<td>EOSINOPHILS</td>
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<td>BASOPHILS</td>
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\[
18100 \times 56\% = 10,136
\]

**ALC = 10,136**
Decline of Total Lymphocyte Count with Age

Lymphocyte Count

Birth  1-4 wk  6 mo  1 yr  2 yr  4 yr  10 yr  21 yr

95th percentile
7300  9100  13500  10500  9500  8000  6500  4800

Median
4200  5600  7300  7000  6300  4500  3100  2500

5th percentile
2000  2900  4000  4000  3000  2000  1500  1000

SCID: Diagnosis

- Repeat CBC w/ manual diff
- Immunoglobulin profile--IgG (may be normal), IgA, IgM, IgE
- More complicated tests needed to confirm:
  - immunophenotyping (flow cytometry)-- T, B, NK cell
  - T- Cell stimulation testing—mitogen and antigen proliferation studies
  - Genetic testing
Laboratory Data

- Lymphopenia

- Abnormal Flow Cytometry: Low number circulating T-Cells and possibly B-Cells and NK cells

- Low immunoglobulin

- Low responses to T-cell Stimulants
Peripheral T&B Cell Immunophenotype

- WBC COUNT
- LYMPHOCYTE
- CLINICAL HISTORY 1
- CD56 (NATURAL KILLER)
- CD8 (CD3+ SUPPRESSOR T-CELL)
- CD19 (B-CELL)
- CD3 (T-CELL)
- CD4 (CD3+ HELPER T-CELL)
- CD4/CD8 RATIO
- ABSOLUTE CD19 (B-cells)
- ABSOLUTE CD3 (T-cells)
- ABSOLUTE CD4
- ABSOLUTE LYMPHOCYTE
- ABSOLUTE CD8
SCID: Special Needs

- CAUTION WITH BLOOD PRODUCTS – Only CMV (-), Irradiated, Leukocyte-reduced
- AVOID LIVE VACCINES – may be fatal
- Monitor for infections
- IVIG infusions
- Isolation
- PCP prophylaxis (TMP/SMX)
SCID: Treatment Options

- **Bone Marrow Transplant**
  - Should be done as soon as possible
  - HLA typing of patient and full siblings

- **Gene Therapy**
Considerations for Adding Tests to the Newborn Screen

- Is there a test available
- Cost issues
- Can you screen with a Physical Exam?
- Does the disease cause serious medical complications
- Is there potential successful treatment?
- Does early intervention lead to better outcome?

Why Screen?

- Children with SCID often look normal at birth
- IF no family history, children often not diagnosed until they have a life threatening infection
- Long term prognosis is much improved in children with SCID if they are diagnosed within the first few months of life.
- Patients with SCID who had BMT <3.5 months of life had much better outcomes
- Survival is only 50-70% if BMT >3.5 months
How to test for SCID on NBS

- CBC/Differential?
- Flow Cytometry?
- TREC(T-cell Receptor Excision Circles)
TRECs

What are they?

- T-cell precursors rearrange their TCR genes during their passage through the thymus. There are excisions of segments of DNA, the ends are ligated to form small circles called T-cell receptor excision circles (TRECs).

- This extra material is excised and winds up in the circulation
TRECs

- Patients with defined primary T cell immunodeficiency diseases have very low T cell numbers and/or T-cell function

- This leads to low or absent number of TRECs formed
TRECs
Considerations for Adding Tests to the Newborn Screen

- Is there a test available
  - Yes- TRECS

- Cost issues
  - Relatively comparable– when children with SCID have BMT earlier, their cost of care is less than children with a BMT later

- Can you screen with a Physical Exam?
  - No children with this disease appear normal- no very obvious physical findings

- Does the disease cause serious medical complications
  - YES- it is fatal in the first 1-2 years of live without BMT

- Is there potential successful treatment?
  - YES- BMT

- Does early intervention lead to better outcome?
  - YES-

Newborn screen

In January 2010, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) recommended to the Secretary of the Department of Health and Human Services, that the Federal government recommend to the States that they include SCID in their newborn screening protocols.

On May 21, 2010, Kathleen Sebelius, Secretary of Health and Human Services (HHS) announced her decision to concur with the committee and add SCID to the core panel of disorders for newborn screenings.
States Currently testing

- 2008- the state of Wisconsin is the first location to add TRECsts to the NBS


* States and territories currently planning to begin screening in 2014: Arkansas, Illinois, Maine, Missouri, Nebraska, North Dakota, Oklahoma, Oregon, Puerto Rico, Rhode Island, South Carolina, South Dakota, Virginia, West Virginia

* States where Advisory Committees have approved adding SCID, but have a longer timetable for implementation: District of Columbia, Georgia, Maryland, North Carolina, New Jersey, Virginia

* From the IDF Website
What have they found

- Children with SCID diagnosed with abnormal newborn screen
- No known missed cases on children who have been screened
- Other severe T-cell diseases found
- Premature infants appear to have more false positive testing. Current discussions on normal levels for this group.
Where is the State of Ohio?

- We went live testing at the end of July

- As of March there has not been a child diagnosed yet with SCID but there have been children with lymphopenia

- Higher proportion of false positives are found in the NICU population
Term Healthy Children Algorithm-
Testing for SCID on the NBS

1st Screen: Abnormal

- 2nd screen to be sent immediately
- No live vaccines, all blood products irradiated/Leukoreduced/CMV negative, avoid exposures to people with fever or infectious symptoms

2nd Screen: Abnormal

- Immediate referral to the closest Pediatric Hospital with Immunology Consultants.

1st Test: Normal
Any subsequent Test: Normal

Low Risk
1st Screen: Abnormal
- 2nd screen to be sent in 2 weeks
- No live vaccines, all blood products irradiated/CMV negative/Leukoreduced, avoid exposures to people with fever or infectious symptoms

2nd Screen: Abnormal
- 3rd screen to be sent in 2 weeks
- No live vaccines, all blood products irradiated, / CMV negative/Leukoreduced/CMV negative avoid exposures to people with fever or infectious symptoms

3rd Screen: Abnormal

1st Test: Normal
Any subsequent Test: Normal

Low Risk

- Order CBC with Differential, T and B-cell peripheral blood immunophenotype and CD45 RO/RA- Send to the closest Pediatric Hospital able to perform the immunology lab testing
- Inform the physician on call for Allergy and Immunology at the closest Pediatric Referral center that the testing has been ordered so they can follow up on blood work
- Allergy and Immunology consult if abnormal- if child at outside NICU, transfer to the Pediatric center for further care/evaluation
Newborn Screening ACT Sheet

Severe Combined Immunodeficiency (SCID) and Conditions Associated with T Cell Lymphopenia

Condition Description: Severe Combined Immunodeficiency (SCID) includes a group of rare but serious, and potentially fatal, inherited immune disorders in which T lymphocytes fail to develop and B lymphocytes are either absent or compromised. Impairment of both B and T cells leads to the term “combined.” Untreated patients develop life-threatening infections due to bacteria, viruses, and fungi. The screening test for T cell receptor excision circles (TREC), a byproduct of normal T cell development, identifies SCID as well as certain related conditions with low T cells. For example, DiGeorge Syndrome with impaired thymus development may cause low T cells and low TREC.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact the family to inform them of the newborn screening result. Point out that additional tests are required to determine whether the baby actually has an immune deficiency.
- Avoid exposing patients to illness pending completion of testing.
- If the infant has any signs of illness, refer to a pediatric hospital right away for evaluation, administration of immunoglobulin and antibiotics.
- If the infant receives transfusions or any blood product, be sure that only leukoreduced, irradiated products that are negative for cytomegalovirus (CMV) are used.
- DO NOT give live attenuated oral vaccine, which could cause serious diarrhea in a baby with SCID. This vaccine is to be given only after an immunology specialist confirms that the baby’s immune system is normal.
- Consult with a specialist in pediatric immunodeficiency diseases (consult with a pediatric allergist/immunologist and/or infectious disease specialist) who will assist with further testing.
- Provide the family with basic information about SCID and T cell lymphopenia (see resource list) and offer or arrange genetic counseling.
- Report confirmatory findings to newborn screening program.

Diagnostic Evaluation: Confirmatory studies include absolute lymphocyte counts, determination of the presence/absence of T and B lymphocytes, and assessment of their function and molecular genetic testing.

The specialist will:

- Order diagnostic tests, likely to include: CBC with differential and lymphocyte subset enumeration.
- Coordinate further testing, antibody levels, lymphocyte proliferation to mitogens, and molecular genetic testing as deemed appropriate.
- Offer disease/genetic counseling.

Clinical Considerations: Immunoglobulin infusions and prophylactic antibiotics are essential to protect against infections. Diarrhea, failure to thrive, otitis media, serious infections (pneumonia, meningitis and/or sepsis), and opportunistic infections commonly occur starting by 2-4 months of life in individuals with SCID. Oral thrush may be seen. Bone marrow hematopoietic cell transplantation may be curative, and outcomes are best if performed within the first 3 months of life or before infections occur. Enzyme replacement and experimental gene therapy are available for some SCID genotypes. The most common form of SCID is X-linked SCID (X-linked SCID), occurring only in males. However, autosomal recessive forms of SCID affect both males and females. Specific gene diagnosis is important for directing therapy as well as providing genetic counseling.

Additional Information:

Genetic Home Reference
SCID.net
National Primary Immune Deficiency Resource Center
Immunodeficiency Foundation

Referral (local, state, regional and national):

Testing
Clinical Services
Find Genetic Services
AAAAI Clinical Services Specialist List
Thank You