Newborn Screening for SCID (Severe Combined Immunodeficiency)

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Disclosures

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this presentation.
- I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.
- Many of references I cite advocate for universal SCID newborn screening in Arizona. I share that opinion and have borrowed extensively from their presentations.
Disclaimer

The opinions expressed are those of the presenter and are not the views of the Indian Health Service or the Department of Health and Human Services.
Objectives

- Describe Severe Combined Immunodeficiency (SCID) - etiology, frequency, natural history, diagnosis and treatment
- Recount the Navajo Experience with SCID
- Review newborn screening for SCID and compare the frequency of SCID with other conditions which are currently being screened
- Compare Arizona to other states with regard to newborn SCID screening
- Examine the costs and the benefits of newborn screening for SCID
Severe Combined Immunodeficiency Syndrome

- Lack of cellular immunity  T-, B- SCID
- Missing T lymphocytes - responsible for defense against viral and fungal infection, facilitate antibody production and recognition of foreign proteins and germs, immune memory cells
- Missing B lymphocytes- make antibodies (immunoglobulins) responsible for processing germs for destruction by other elements of the immune system, give immune memory against many infections
- Bacterial, viral, fungal infections can all become lethal, even in spite of antimicrobial treatment
Signs and Symptoms

- Usually are born appearing normal
- Mouth ulcers/perianal ulcers
- Recurrent thrush
- Failure to gain weight
- Recurrent diarrhea
- Skin rash
Outcomes and Complications

- Inability to fight off infection acquired in the first year of life
- Recurrent common infections and occurrence of unusual infections
- Usually fatal by age 2 if not treated
  - Exposure to non-irradiated blood product transfusions
  - Live vaccines (which is a concern to pediatricians)
  - Common infections
Etiology of SCID

Mutations in one of at least 13 different genes can cause SCID

What is the frequency?

From other states experience, it can be as common as 1:58,000 live births
Treatment of SCID

- Bone marrow transplant
- Peripheral stem cell transplant
- Umbilical cord blood transplant
  - All are a source of the stem cells that eventually will mature into lymphocytes
  - Donor- usually a sibling or parent
  - Bone Marrow Transplant services available in AZ and CA

(Note: HCT or HSCT - Hemopoietic stem cell transplant)
Prior to Newborn Screening (Navajo Experience)

Screening tests - CXR (absent thymus), CBC with ALC (absolute lymphocyte count)
If suspected
- Lymphocyte subsets and function tests
- Required live cells and 8 ml blood (in an infant)
- Required Fed Ex to reference lab
- Potential delay of 1-2 weeks to get results back
- Cost ~$800
Frequent Problem

Infection by viruses such as CMV (cytomegalic inclusion virus) which then makes stem cell transplants less effective and could also be a cause of death.
Why is SCID more common in American Indians in Arizona?

Thought to be due to the “Founder Effect”
Founder Effect

A gene rare in the general population occurs in a small, isolated, rapidly expanding population which leads to increased gene frequency and increased frequency of the disease in that population.
WHO (World Health Organization) Criteria for Screening

- The condition is an important health problem
- The cost of case finding reasonable
- It is recognizable in latent phase
- Effective treatment is available
- It is acceptable to population tested
Severe Combined Immunodeficiency meets the criteria

- A lethal disorder not detectable at birth by routine examination
- Death comes from overwhelming infection in infancy
- Incidence of disease is significant in the US but especially in AZ
- TREC testing now available to screen patients
- Cost per test as low as $6 per test commercially
- Confirmatory testing available
- Flow cytometry
- Treatment available- potentially curative
- Stem cell transplant
- Gene therapy
Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children - Criteria for Recommendation for Routine Newborn Screening

1. The disorder has to be considered medically serious
2. There should be prospective pilot data from population-based screening
3. The spectrum of the disorder should be well described in the medical literature
4. The screening test characteristics should be reasonable, including having a low rate of false-negative results
5. If the spectrum of the disorder is broad, those most likely to benefit from treatment should be identifiable
6. There has to be an effective treatment that is given before the infant becomes symptomatic
Newborn Screening for SCID

Effort to find a method utilizing “blood spot”
TREC (T cell Receptor Recombination Excision Circles)

- A biomarker for Thymic T Cell Production
- Extra DNA that is “snipped out” when making the DNA sequence that codes for a unique receptor
  - Part of normal T cell maturation
  - The numbers of TRECs are a reflection of the population of recently formed T cells in the blood
Newborn Screening in Arizona

Endocrine Disorders (2)
- Congenital hypothyroidism (CH)
- Congenital adrenal hyperplasia (CAH)

Amino Acid Disorders (6)
- Phenylketonuria (PKU)
- Maple syrup urine disease (MSUD)
- Homocystinuria (HCY)
- Citrullinemia (CIT-1)
- Argininosuccinic acidemia (ASA)
- Tyrosinemia type I (TYR-1)
Newborn Screening in Arizona (cont’d)

Fatty Acid Oxidation Disorders (5)

- Carnitine uptake defect (CUD)
- Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
- Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
- Trifunctional protein deficiency (TFP)
Newborn Screening in Arizona (cont’d)

Organic Acid Disorders (9)

- Isovaleric acidemia IVA)
- Glutaric acidemia type I (GA-1)
- 3-Hydroxy-3-methylglutaric aciduria (HMG)
- Multiple carboxylase deficiency (MCD)
- Methylmalonic acidemia (Cbl A,B)
- Methylmalonic acidemia-mutase deficiency (MUT)
- 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
- Propionic acidemia (PROP)
- Beta-ketothiolase deficiency (BKT)
Newborn Screening in Arizona (cont’d)

Hemoglobin Disorders (3)
- Sickle cell anemia (Hb SS)
- S, beta-thalassemia (Hb S/β Th)
- S,C disease (Hb S/C)

Other Disorders (3)
- Biotinidase deficiency (BIOT)
- Galactosemia (GALT)
- Cystic Fibrosis (CF)
Newborn Screening in Arizona (cont’d)

Disorders not detected by bloodspot screening (2)

- Hearing Loss (HEAR)
- Critical Congenital Heart Disease (CCHD)
## Frequency of Diseases on AZ Newborn Screen

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
<th>Treatment/Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Hypothyroidism</td>
<td>1:4,000</td>
<td>Supportive Care (MR if not treated)</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia</td>
<td>1:15,000 Caucasians</td>
<td>Supportive care; Death if not identified</td>
</tr>
<tr>
<td></td>
<td>1:280 Native Americans</td>
<td></td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>1:12,000</td>
<td>Supportive care, severe MR</td>
</tr>
<tr>
<td>Maple Syrup Urine Disease</td>
<td>1:185,000 Caucasians</td>
<td>Death due to neurologic damage/supportive care</td>
</tr>
<tr>
<td></td>
<td>1:380 Mennonite</td>
<td></td>
</tr>
<tr>
<td>Homocysteinuria</td>
<td>1:60,000</td>
<td>Supportive care, death due to thromboembolism</td>
</tr>
<tr>
<td>Citrullinemia type 1</td>
<td>1:57,000</td>
<td>Hyperammoniemia/encephalopathy and death, supportive care</td>
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<td>Argininosuccinic Acidemia</td>
<td>1:70,000</td>
<td>Dietary restriction/supportive care</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>1:100,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>Carnitine uptake Defect</td>
<td>1:50,000</td>
<td>Supportive care/Death if not identified</td>
</tr>
<tr>
<td>MCAD</td>
<td>1:4,000-1:17,000</td>
<td>Supportive care/Death if not identified</td>
</tr>
<tr>
<td>VLCAD</td>
<td>1:30,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>LCHAD (Finnish)</td>
<td>1:62,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>LCHAD (lower in U.S.)</td>
<td></td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>Isovaleric Acidemia</td>
<td>1:250,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>Glutaric Acidemia type 1</td>
<td>1:35,000</td>
<td>Supportive care/death if not identified</td>
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<td>3-Hydroxy-3-methylglutaric aciduria</td>
<td>&lt;1:100,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency</td>
<td>1:100,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>MMA-cobalamin defect</td>
<td>1:100,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>MMA-mutase deficiency</td>
<td>1:37,000 (Hispanic)</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>MMA-mutase deficiency</td>
<td>1:50,000-1:100,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>3MCC deficiency</td>
<td>1:36,000-1:50,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>Proprionic acidemia</td>
<td>1:100,000</td>
<td>Supportive care/death if not identified</td>
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<td>Beta-ketothiolase deficiency</td>
<td>&lt;1:1,000,000</td>
<td>Supportive care/intellectual disabilities if not treated</td>
</tr>
<tr>
<td>HbSS</td>
<td>1:375 African Americans</td>
<td>Supportive care/HCT/Death if not treated</td>
</tr>
<tr>
<td>HbS/beta-thalassemia</td>
<td>1:1,667 African Americans</td>
<td>Supportive care/HCT/Death if not treated</td>
</tr>
<tr>
<td>HbSC</td>
<td>1:835 African Americans</td>
<td>Supportive care/HCT/Death if not treated</td>
</tr>
<tr>
<td>Trifunctional protein deficiency</td>
<td>Unknown</td>
<td>Supportive care/still can die if treated</td>
</tr>
<tr>
<td>Biotinidase Deficiency</td>
<td>1:61,000</td>
<td>Supportive care/death if not identified</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1:50,000</td>
<td>Supportive care/neurologic defects and death if not identified</td>
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<td>Cystic Fibrosis</td>
<td>1:2,500</td>
<td>Supportive Care/death around age 40</td>
</tr>
<tr>
<td>Critical Congenital Heart</td>
<td>1:4,800</td>
<td>Cardiac surgery/death if not identified</td>
</tr>
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</table>

Incidence of SCID is 1:58,000 in general American Population, and 1:3,000 in Native Population

Treatment is HCT (hematopoietic [stem] cell transplant) - survival >90% if transplanted early regardless of donor source.
Newborn Screening Strategies

- **Universal Screening**
  - The strategy which is advocated by Immune Deficiency Foundation, Drs. Buckley, Puck, Hu and others

- **Targeted Screening**
  - Navajos and Apaches - but many women deliver off reservation
  - If newborn screening were just performed on Navajos and Apaches, would miss the other cases of SCID
Newborn Screening for SCID In AZ

- Currently only being performed on patients born on the Navajo reservation (1,296 births in 2014; but 85,252 additional births in AZ in 2014)
- Estimated prevalence of SCID nationally 1:58,000
- Prevalence of SCID in Navajo is 1:3,269
- Because of increased Native American population in the state of AZ, AZ would be expected to have greater than the national average for SCID diagnoses

Why Not Add SCID to Arizona Newborn Screening?

- SCID is a rare/heterogeneous disorder
  - Fortunately TREC assays can capture more diseases than just SCID!
- SCID has a definitive, curative treatment that when it is identified early is much more successful
Five year survival for Typical SCID depends more on infection than age at HCT (Hematopoietic [Stem] Cell Transplantation)
SCID Newborn Screening: Current Status of Implementation Map
42 States Currently Screening for SCID - 88% of all newborns in the U.S. are receiving SCID screening

As of October 1, 2016

Screening
Pilots and Planning in 2016 and 2017
Not Screening
The Problem with Not Performing Newborn Screening for SCID

- The major issue is the patients will still require expensive medical care and will die at an early age in spite of that expensive care
- Ethical as well as economic implications
Cost and Survival Rate for Early Treatment

Cost of early treatment (within first 3.5 months) before infections develop can be as low as $50,000 per infant.

Newborn Screening for Severe Combined Immune Deficiency (SCID) - IDF Fact Sheet for SCID NBS in Arizona
Cost and Survival Rate for Late Treatment

- Over $2,300,000 for treatment of one Arizona baby born off of reservation in 2015.
- Early infections often lead to lifelong medical complications.
- The survival rate drops to less than 70% for infants who are transplanted after the first 3.5 months of life.

Newborn Screening for Severe Combined Immune Deficiency (SCID) - IDF Fact Sheet for SCID NBS in Arizona
Cost of Newborn Screening Test

- A newborn screening test has been developed and recommended by the U.S. Department of Health and Human Services and the CDC as the preferred way to screen newborns for SCID.

- The test, called TREC, can be done using the same methods as other newborn screening tests and has an estimated cost of $6 per infant screened from the vendor that Arizona Department of Health anticipates using.
Fiscal Costs/Benefits for Arizona

- Cost for FDA approved test kit: $6.00 x 90,000 live births = $540,000.
- Cost to the Arizona Medicaid program, Arizona Health Care Cost Containment System (AHCCCS) = $270,000.
- Savings per identified and treated newborn with SCID: $2 million.
- At an estimated 2-4 infants born with SCID in Arizona, with at least one of which would be Medicaid covered, the state would recover its cost for test kits and save state budget $2 million every year by diagnosing early.

Newborn Screening for Severe Combined Immune Deficiency (SCID) - IDF Fact Sheet for SCID NBS in Arizona
Credits

- Slide of oral thrush - Dr. Jennifer Puck presentation
- Slides of Comparisons of Diseases on AZ Newborn Screen and Newborn Screening for SCID in Arizona - Dr. Holly Miller presentation
- Slide of blood spot from Dr. Hu’s presentation
- Navajo information from Dr. Diana Hu
Resources

- [http://primaryimmune.org/treatment-information/newborn-screening/](http://primaryimmune.org/treatment-information/newborn-screening/)