Severe Combined Immunodeficiency (SCID)

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Outcomes without screening:
Severe combined immunodeficiency (SCID) is a genetically heterogeneous group of inherited disorders that cause severe defects in the immune system. Though there are many different genetic mutations that cause different phenotypes, all patients with SCID have abnormalities in T cell development and maturation. They can also have problems with B and NK cells, either due to their genetic mutation or due to the inability of the abnormal T cells to perform their typical helper function and help B cells. This is why it is called combined immunodeficiency. SCID results in serious, often fatal infections within the first year of life. Babies with SCID often do not survive infancy without stem cell transplant, gene therapy or enzyme replacement. Transplant outcomes and survival are best if performed before age 3 months or before the first serious infection.

Babies with SCID typically look normal at birth and do not show any outward signs of their immune dysfunction. They are typically identified only after they have had a serious viral, bacterial, or fungal infection, or if they have failure to thrive or chronic diarrhea. Due to the importance of identifying these babies before they have a serious infection, the state of TN is adding SCID screening to the newborn screening panel starting January 1, 2016.

Incidence:
The incidence of SCID is estimated to be 1: 50,000-100,000 live births. It affects all ethnic populations.

Outcome with screening:
Based on studies looking at the outcomes of patients with SCID who are identified and treated early and those who are identified and treated later, it is clear that outcomes are improved with early diagnosis and treatment. Since SCID is not obvious early on, these babies are not protected from infections and may also have difficulty with growth and gaining weight. Newborn screening will allow us to identify babies with SCID early and institute protective treatments to limit and prevent infections prior to transplant.

Causes of SCID:
A number of separate genetic disorders comprise SCID, each one affecting T cell development in some form. These genetic mutations can be X-linked or autosomal recessive and can occur in a variety of different signaling molecules or cytokine receptors. The most common form of SCID is X linked and is caused by a mutation in a cytokine receptor chain, which is common to several cytokines involved in immune development.

When T cells do not develop properly, they cannot perform their helper function for B cell growth and proper development. Therefore, the B cells do not produce antibodies normally.

Depending on where the mutation is, NK cells may also be affected. These cells are very important in defense against viral infections.

Treatment:
Babies with SCID require early identification in order to institute infectious protection. This includes protective isolation, in the home if this is deemed safe, or in the hospital. These babies should be started on immunoglobulin replacement since they do not make antibodies on their own. They will also require antibiotic prophylaxis for *Pneumocystis pneumoniae* once they reach 1 month of age. They should be referred for transplant as soon as the diagnosis is made.

Screening tests and confirmation:
The screening test for SCID is via PCR analysis of T-cell receptor gene excision circles or TREC. This test detects a by-product of normal T cell development. The absence or decreased number of TREC indicates T cell impairment, possibly due to SCID. Other forms of T cell lymphopenia, like DiGeorge syndrome will also have low TREC values.

When a low TREC value is obtained, confirmatory testing is required. This will include a CBC with differential and flow cytometry for T, B and NK cell numbers. Based on the results of these tests, further testing, including genetic testing may be indicated.

Special Concerns and Issues:
Newborn screening TREC analysis will identify children with T cell lymphopenia from causes other than SCID as well. These include DiGeorge syndrome, ataxia-tel angiectasia, congenital cardiac disease, congenital anomalies such as CHARGE syndrome, and prematurity. Notably, premature infants often have low T cell numbers related to their prematurity and immune immaturity, rather than from an immunodeficiency. Therefore, their TREC levels may be low initially but most will normalize as they mature.

Some forms of SCID do not result in low TREC values initially, so babies with frequent or severe infections should be worked up for immunodeficiency, regardless of a normal NBS result.