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Expert Commentary: Practical Issues in Newborn Screening for Severe Combined Immune Deficiency (SCID)

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Kate Sullivan: We asked experts in the field to comment on some of the more pressing questions in the burgeoning field of newborn screening for severe combined immune deficiency (SCID). Their valuable perspectives are provided to guide the establishment of policies as additional states consider and implement newborn screening for SCID. Jennifer Puck has been a strong advocate for newborn screening and originated the concept of T cell receptor excision circle (TREC) screening using dried blood spots; the TREC assay has been performed on all newborns in California since August 2010, and Dr. Puck is the immunology consultant for the California Genetic Disease Lab; she has instituted a centralized follow-up model, with the screening program obtaining and sending follow-up tests throughout the state to a single immunology lab. Dr. Puck and her Southern California colleague, Dr. Joseph Church, interpret all flow cytometric results from a designated laboratory with a standardized analytic panel. Dr. Jack Routes was responsible for implementing the first state newborn screening program for SCID, which started in Wisconsin in January 2008. Wisconsin is a leader in the field of newborn screening. Dr. Alexandra (Lisa) Filipovich has developed Cincinnati Children's Hospital into one of the preeminent transplant centers. Novel protocols to limit toxicity and improve outcomes are central to the innovations at Cincinnati Children's Hospital.

Commentary

It is well accepted that SCID patients treated with hematopoietic cell transplantation early in life have the highest likelihood of long-term survival. This is largely due to a lower burden of acquired infections, which can limit the ultimate success of the transplant procedure, as well as the less clearly defined belief that very young infants are more accepting of allogeneic stem cells and do not have as severe graft versus host disease as those treated at an older age. The long-anticipated advent of early diagnosis of life-threatening T cell disorders, using TREC quantitation, has arrived in several parts of the USA.

The TREC test is an excellent biomarker for the number of naive T cells that have recently emigrated from the thymus. Infants with low or absent TRECs may have inadequate thymic production of autologous T cells or excessive losses of such cells from the peripheral blood, which is sampled to make dried blood spots for TREC T to quantitation using real-time PCR. Importantly TRECs are non-replicating and become diluted during T cell division. As a result, allogeneic cells, such as maternal cells, as well as autologous cells that may have undergone oligoclonal peripheral expansion, such as in Omenn syndrome, do not confound the TREC test.

Historically, SCID patients could be transplanted only if they had an HLA-identical sibling donor, and this is still the optimal treatment. Use of haploidentical parental donors for T cell-depleted SCID transplants without preconditioning made every SCID infant a candidate for transplantation treatment. While this has been life saving in many cases, long-term follow-up from a number of centers has revealed incomplete immune reconstitution of B cell function in the majority of patients, and some patients experience a waning immune repertoire associated with poor/undetectable myeloid engraftment. Chronic complications such as graft versus host disease with wasting and disseminated warts 10 to 20 years post-transplant have also been described. Conditioning has been advocated by some as a strategy to improve the rate of full donor chimerism, but outcome data currently are limited. Furthermore, the growth of unrelated donor registries has now made it possible to find excellent HLA-matched donors for most SCID patients. However, there is currently no consensus as to the most effective and uniformly safe protocols for infants whose metabolic immaturity may leave them at risk for toxicity from chemotherapy or who have a type of SCID associated with radiosensitivity. Indeed, a single conditioning protocol may not be best for all genotypes. Therefore, immunologic and genetic evaluations after a positive TREC test are critically important.

SCID has been called a medical emergency. It is critical to have infants with severe T cell impairment evaluated on an urgent basis and managed by an immunologist familiar with SCID. Although definitive treatment may not be instituted for several weeks, immediate intervention is to maintain the infant under close observation in an isolated environment, to avoid live vaccines, to prevent the use of non-irradiated blood, and to give immunoglobulin and prophylactic antibiotics to prevent *Pneumocystis* and other infections. In cases where there is no known family history of SCID, a stepwise process is begun toward a definitive diagnosis and treatment. A fresh sample for flow cytometry should be analyzed to enumerate the numbers of T cells, B cells, and NK cells, and for examining the distribution

of naive/memory (e.g., CD45RA/RO) T cells. If the flow cytometry is abnormal, this is followed by referral to a pediatric immunologist. Further testing to specifically define the underlying defect may take months, and if a suitable family donor is not identified, securing an unrelated donor also takes time. Nevertheless, rapid definition of the type of immune deficiency is essential although the specific gene mutation is not required in most cases to begin a transplant protocol.

Not every infant with a positive SCID screen will require transplantation, however. Every population-based newborn screening test for a condition previously understood only from the perspective of clinical cases has revealed unexpected findings among individuals with abnormal screening results. The TREC assay has detected infants who have T lymphopenia but do not have classical SCID as defined by the Primary Immune Disease Treatment Consortium as <300 T cells/ μ L and $<10\%$ of normal PHA proliferative responses. Such T lymphocytopenic infants may have (1) leaky mutations in recognized SCID genes; (2) severe phenotypes associated with gene defects that generally cause less profound T cell deficiency, such as CHH, DOCK8, NEMO; or (3) variants of SCID with undetermined genetic cause. Since genotyping is slow, laborious, and expensive, and many rare disease genes are not sequenced in clinical labs, it is challenging to arrive at a molecular diagnosis for these infants. There are also infants with secondary T lymphocytopenia and with syndromes such as DiGeorge or CHARGE that can be associated with low T cells. Identification in the early weeks of life before any infectious complications have occurred provides important protection for the patient from the harm of infection but removes a critical element of the phenotype when it comes to establishing the need for transplantation therapy. The infant may thrive in good health, often with immunoglobulin and antibiotic treatments that potentially obscure the natural trajectory of the condition. In these uncharted waters, it is incumbent on the immunodeficiency experts caring for the infant to pursue lymphocyte functional studies while carefully following clinical exam and lab values over time. Transplantation outcomes in SCID are generally good, but fatalities occur, and transplantation should not be performed without demonstration of serious defects of lymphocyte function.

In Table I, the current practices for specific settings are detailed. This field is rapidly evolving, and as highlighted above, there are situations where the intervention strategy may not be well defined. These guidelines represent a forum for ongoing discussions and refinement.

Table I

Current practices for specific settings

Issue	Jennifer Puck	Jack Routes	Alexandra Filipovich
Low TRECs in a premature infant	If a replicate is low, the baby is referred for flow cytometry.	TRECs are repeated until >37 weeks corrected gestational age; if low at that point, referral is made to an immunologist.	Reassessment when the baby reaches term.
The ideal time interval between a positive TREC result and a formal immunologic assessment	Under 2 weeks, less if TRECs are undetectable; a baby with low TRECs should not receive live vaccines.	Within 2 weeks. (The mean time from any abnormal TREC assay to flow cytometric evaluations in Wisconsin is about 7 days; if the TREC is zero, the mean time is 2 days.) If the TREC is zero, the family is cautioned to avoid sick contacts and isolate the baby.	2 weeks. The family should be cautioned to isolate and protect the baby
The ideal time between the definitive diagnosis of SCID and transplantation	2 weeks to 4 months. The workup is overseen by a designated Immunology Referral Center, which coordinates referral to a transplant center.	Once the diagnosis is established, a referral is made to a transplant center. The timing is dictated by donor availability.	3–6 months
If the gene defect is not known, is the transplant protocol modified to accommodate potential DNA repair defects?	Radiation sensitivity testing is available for all California SCID infants. DNA damaging conditioning regimens are particularly dangerous in patients with radiation-sensitive SCID.	Reduced intensity conditioning is preferred. Infants without a molecular diagnosis are tested for radiation sensitivity, although if clinically indicated, transplantation is not delayed based on the pending results.	Reduced intensity conditioning is preferred.