seek help for symptoms (presentation delay) and health care providers to be unaware of the presenting symptoms and not order confirmatory laboratory tests (diagnostic delay).

REVIEWER COMMENTS. When young children present with ataxia, an easy and inexpensive test to obtain is α-fetoprotein (AFP), which is rarely normal in A-T; this may improve earlier diagnosis of A-T.

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Risk Factors and Clinical Significance of Lymphopenia in Survivors of the Fontan Procedure for Single-Ventricle Congenital Cardiac Disease

Morsheimer MM, Rychik J, Forbes L, et al. *J Allergy Clin Immunol Pract*. 2016;4(3):491–496

PURPOSE OF THE STUDY. To determine the clinical significance of immunologic laboratory anomalies (lymphopenia and hypogammaglobulinemia) commonly seen in survivors of the Fontan procedure for single-ventricle congenital heart disease.

STUDY POPULATON. The study included 178 patients ages 3 to 26 years with congenital single-ventricle cardiac anomaly (status: postcompletion of surgical repair) with Fontan who had established outpatient care in the Single Ventricle Survivorship Program (SVSP) at the Children's Hospital of Philadelphia.

METHODS. This was a retrospective chart review of the immunologic parameters of patients enrolled in the SVSP. Data on demographics, diagnoses, surgical interventions, immunologic laboratory data, and medications were gleaned from the electronic medical records. SVSP and immunology consult notes were reviewed for infectious history, absolute lymphocyte count (ALC), and IgG levels. A P value of $<.05$ was considered statistically significant.

RESULTS. Most SVSP patients had some degree of lymphopenia. Those with protein-losing enteropathy (PLE) had lower median ALC and IgG levels (672 cells/μL and 200 mg/dL, respectively) than those without (1610 cells/μL and 868 mg/dL, respectively). Approximately 12% of those in the non-PLE group had significant asymptomatic lymphopenia (ALC $<$1000 cells/μL). In a logistic regression analysis, PLE and increased number of years after Fontan were found to be the only significant risk factors for lymphopenia. Despite lymphopenia in the majority, few participants were significantly clinically affected; 24% had a delayed clearance of cutaneous viral infections, 63% had atopy, and 1 died of EBV-associated Hodgkin lymphoma. Severe opportunistic infections typical of cellular immune defects were not observed, even among those with significant lymphopenia.

CONCLUSIONS. Patients with repaired single-ventricle physiology often demonstrate T-cell lymphopenia and hypogammaglobulinemia. The most common clinical manifestation was a delayed clearance of cutaneous viral infections. Significant systemic opportunistic infections were not seen despite laboratory abnormalities and a lack of antimicrobial prophylaxis or immunoglobulin replacement.

REVIEWER COMMENTS. Patients with repaired single-ventricle physiology often demonstrate T-cell lymphopenia and hypogammaglobulinemia. The exact mechanism by which this occurs is unclear, but it is seen in patients both with and without PLE. A proposed mechanism that is unique to this population is chronic venous hypertension leading to chronic low-level lymph loss in the gut with resultant lymphopenia. Further studies will be needed to better understand the impact of congenital heart disease on lymphocyte development, function, recirculation, and long-term survival. This study provides reassurance that morbidity associated with these immunologic changes is limited.

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CRISPR/Cas9 β-globin Gene Targeting in Human Haematopoietic Stem Cells

Dever DP, Bak RO, Reinisch A, et al. *Nature*. 2016;539(7629):384–389

PURPOSE OF THE STUDY. Sickle cell disease (SCD) is caused by a single nucleotide mutation (A to T) in the β-globin *(HBB)* gene leading to a Glu6Val amino acid change. The purpose of this study is to show that this gene can be effectively edited in human hematopoietic stem and progenitor cells (HSPCs) using the CRISPR/Cas9 system and to develop a method to enable efficient engraftment of edited human cells in mice.

STUDY POPULATION. HSPCs from mobilized peripheral blood of healthy donors and SCD patients were used for gene editing ex vivo. Immune-deficient NSG mice were used as recipients of edited HSPCs.

METHODS. Cas9 protein can generate double-strand breaks in DNA that can then be repaired by nonhomologous end joining or homologous recombination (HR) if a donor strand is provided. HSPCs were electroporated with Cas9 protein combined with sgRNA (Cas9 RNP) targeting the *HBB* gene. Cells were then infected with recombinant adeno-associated viral vectors of serotype 6 (rAAV6) carrying a donor sequence with a single nucleotide mutation (A to T) in the *HBB* gene and a green fluorescent protein (GFP) sequence or truncated nerve growth factor receptor (tNGFR) expression cassette. tNGFR is expressed at the surface of transfected cells and allows for enrichment of transduced cells by utilizing magnetic bead–based

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