eosinophils, which are uncontrolled by high-dosage ICS plus LABA.

REVIEWER COMMENTS. This is the first phase 3 study of benralizumab, which acts against interleukin-5 (IL-5) receptor α and induces direct, rapid, and near-complete depletion of eosinophils. Because it acts differently than mepolizumab and reslizumab and is effective with Q8W dosing, benralizumab may be an additional option in this asthma population.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2017–2475LLLL

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Improved Control of Childhood Asthma With Low-Dose, Short-term Vitamin D Supplementation: A Randomized, Double-blind, Placebo-controlled Trial

Tachimoto H, Mezawa H, Segawa T, Akiyama N, Ida H, Urashima M. *Allergy*. 2016;71(7):1001–1009

PURPOSE OF THE STUDY. To assess whether low-dose, short-term vitamin D supplementation in addition to standard treatment improved control of childhood asthma.

STUDY POPULATION. Eighty-nine Japanese schoolchildren ages 6–15 years who had a diagnosis of asthma based on GINA criteria and spirometry were randomly assigned to receive vitamin D ($n = 54$) or a placebo ($n = 35$). Ninety-four percent of subjects were using either an inhaled corticosteroid or a leukotriene receptor antagonist at baseline. The median vitamin D level at baseline was 29 ng/mL.

METHODS. Collaborating pediatricians who examined the subjects at baseline, 2 months, and 6 months were blinded to vitamin D_3 (800 IU/day) or placebo treatment throughout the study. Subjects were assessed for asthma control as the primary outcome by GINA guidelines at these time points. Adherence to treatment was evaluated. Levels of serum 25(OH)D, serum IgE, and selected allergen-specific IgE levels were measured.

RESULTS. At 2 months, asthma control by GINA guidelines was significantly improved in the vitamin D group compared with the placebo group ($P = .015$). Childhood asthma control test (CACT) scores (a secondary outcome) were similarly improved at 2 months ($P = .004$) and 6 months ($P = .012$) in the vitamin D group versus the placebo group. Fewer subjects in the vitamin D group (15%) had a peak expiratory flow rate of <80% compared with the placebo group (34%) at 6 months ($P = .032$).

CONCLUSIONS. Low-dose, short-term vitamin D supplementation in addition to standard treatment may improve levels of asthma control in schoolchildren.

REVIEWER COMMENTS. There are contrasting studies in the area of vitamin D supplementation and asthma. The strengths/novelty of this study are as follows: (1) it is a randomized, double-blind, placebo-controlled trial; (2) it involves children who are on controller therapies; and (3) it includes subjects who are not as deficient in vitamin D as those in other studies. The results support further investigation in this area to examine different doses and durations of vitamin D supplementation and the potential seasonal benefit in controlling asthma.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2017–2475MMMM

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PRIMARY IMMUNODEFICIENCY

Ataxia Telangiectasia: Presentation and Diagnostic Delay

Devaney R, Pasalodos S, Suri M, Bush A, Bhatt JM. *Arch Dis Child*. 2017;102(4):328–330

PURPOSE OF THE STUDY. Ataxia-telangiectasia (A-T) is a rare, inherited, multisystemic disease involving the nervous, immune, and respiratory systems. The purpose of this study was to determine if there is a delay in presentation and diagnostic confirmation in children who are eventually diagnosed with A-T.

STUDY POPULATION. A total of 79 children attending the National Pediatric A-T Clinic in Nottingham, England, seen since 2009 were included.

METHODS. Data were collected by retrospective chart review and included the age of initial symptoms, age at first presentation to any health care provider, age when α-fetoprotein (AFP) was measured, and age when genetic diagnostic confirmation was made. Presentation delay was the time between the first concern by parents and the first presentation to health care providers, and diagnostic delay was the time between presentation to health care providers and genetic confirmation of the diagnosis.

RESULTS. A total of 71 children (90%) initially presented with ataxia, 16% presented with recurrent infections, and 5% presented with ocular telangiectasias. The median age at the first symptoms was 18 months (range 6–94 months); the median age at the first presentation to health care providers was 29 months (range 10–127 months). The median presentation delay was 8 months (range 0–118 months). The median time of AFP measurement was 60 months (range 23–221 months). All children had genetic confirmation at a median age of 51 months (range 25–178 months). The median diagnostic delay was 12 months (range 1–109 months). Nearly 40% of the children had a confirmatory diagnosis at the age of 5 years or older.

CONCLUSIONS. Significant delays were seen in the presentation and diagnostic confirmation of A-T. This may be due to a lack of awareness of this rare condition, leading parents to not

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.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2017–2475NNNN

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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.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2017–2475OOOO

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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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Pediatrics 2017;140;S225
DOI: 10.1542/peds.2017-2475NNNN

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Pediatrics 2017;140;S225
DOI: 10.1542/peds.2017-2475NNNN