

Treatment of a 4-year-old boy with mepolizumab for lymphocytic hypereosinophilic syndrome



A previously healthy 4-year-old boy presented to the emergency department with 2 days of headache, unsteady gait, and left hemiparesis. Emergent head computed tomography revealed a right-sided hypodensity concerning for ischemic stroke. Follow-up magnetic resonance imaging and magnetic resonance angiography revealed multiple acute ischemic foci in the right middle cerebral artery and posterior cerebral artery watershed territories, chronic appearing ischemic foci bilaterally, and bilateral carotid artery narrowing concerning for medium or large vessel vasculitis. Cardiac, hypercoagulability, and rheumatologic workup were unrevealing. Vasculitis workup was also negative, with normal erythrocyte sedimentation rate, C-reactive protein, MPO, PR3, C3, and C4. Blood vessel biopsy was deferred owing to negative laboratory workup and lack of systemic inflammatory symptoms. He received aspirin 81 mg daily and discharged home 1 week later.

During hospitalization, he was noted to have leukocytosis (white blood cell count 20,600/mm³) with eosinophilia ranging from 2650 to 7250/mm³. Results of an infectious disease workup were negative. Malignancy was considered, but flow cytometry of the blood was normal, and bone marrow biopsy with flow cytometry and cytogenetics was also normal. He was profoundly anemic, with hemoglobin of 4.3 g/dL on admission. He received blood and intravenous iron, and his hemoglobin improved to 8.8 g/dL at discharge. At his 1-month follow-up, his eosinophilia persisted at 3170/mm³, and he was referred to Allergy and Immunology for further evaluation.

Eight weeks later, at the time of his initial Allergy and Immunology visit, he had made a full neurologic recovery and his hemoglobin had normalized. Initial history was unrevealing; he had no history of asthma, rash, abdominal pain, nausea, vomiting, diarrhea, or recurrent infections. Family history was negative for atopy, autoimmunity, or immune deficiency. The boy lived in a rural area with 2 dogs and 2 cats, with ducks, geese, and turkeys on the property. There were frequent visits to a grandmother who raised pigs. Notably, before admission, his mother observed him eating dirt.

Immune evaluation results revealed persistent eosinophilia (6869/mm³) and mildly elevated immunoglobulin E (122.0 IU/mL), but normal serum tryptase, troponin T, vitamin B12, and computed tomography chest, abdomen, and pelvis. Cytogenetic fluorescence in situ hybridization was negative for FIP1L1/PDGRFRA. Serology results for *Toxocara*, *Ascaris*, *Trichinella*, and *Strongyloides* were negative. Stool ova and parasite panel with trichrome stain was also negative.

Flow cytometry revealed elevated absolute numbers of total CD3⁺ T cells (5455/mm³, reference range 1400–3700/mm³), CD3⁺CD4⁺ T cells (3198/mm³, reference range 700–2200/mm³), and CD3⁺CD8⁺ T cells (2006/mm³, reference range 490–1300/mm³). A T-cell receptor clonality assay revealed polyclonal amplification with multiple distinct peaks in an oligoclonal distribution. On this basis, along with a negative extensive workup for other etiologies, a diagnosis of lymphocytic-variant hypereosinophilic syndrome (L-HES) was made.

The boy was prescribed 20 mg (1.25 mg/kg) oral prednisolone with good response 1 week after (absolute eosinophil count [AEC] 130/mm³) (Fig 1). A weekly steroid taper was attempted, but his eosinophils rebounded at the 10 mg dose. Fortunately, his symptoms did not recur. He subsequently required 20 mg daily for control. Unable to taper his steroids further, a steroid-sparing alternative was pursued.

The interleukin-5 antagonist mepolizumab is the only biologic medication approved to treat HES, and it has been found to decrease eosinophil counts and the need for steroid therapy to less than

10 mg/d in 95% and 84% of patients, respectively.¹ However, mepolizumab is approved by the Food and Drug Administration only for adults and children 12 years or older at a dose of 300 mg every 4 weeks. There are small case reports of pediatric patients treated with mepolizumab for HES with success,^{2–4} but the youngest of these was an 8-year-old boy. The youngest reported pediatric patient we could find treated with mepolizumab for any indication was a 5-year-old boy treated for eosinophilic bronchiolitis.⁵ In all cases, patients responded to treatment with a favorable safety profile.

With this in mind, we decided on a reduced dose of 100 mg (6 mg/kg) mepolizumab injected subcutaneously every 4 weeks. This dose was chosen based on previous studies in pediatric patients that used up to 10 mg/kg⁶ and for pragmatic reasons, specifically the availability of commercially available injection devices. The boy tolerated the injection well and had no adverse effects. One week after his first dose, his AEC dropped sharply to 10/mm³, and we were able to taper his corticosteroids off completely with sustained response. Thereafter, his AEC has remained within normal limits with only the monthly mepolizumab (Fig 1).

Herein, we report a case of a young boy aged 4 years with L-HES treated successfully with 100 mg mepolizumab subcutaneously every 4 weeks. To the best of our knowledge, our patient is the youngest reported to receive mepolizumab for any indication. He has experienced no adverse effects and has been able to wean completely off corticosteroids. Moving forward, we plan to monitor eosinophil counts every 3 to 6 months, including yearly blood flow cytometry to monitor for progression to T-cell lymphoma. Hypereosinophilia has also been recognized as a manifestation of immunodeficiency in pediatric patients, often with higher peak AECs (>5000/mm³) as in our patient,⁷ so genetic testing for inborn errors of immunity will also be pursued.

HES can be associated with neurologic symptoms and has been reported to cause strokes in arterial watershed territories,⁸ possibly secondary to thromboembolic events or vascular inflammation related to endothelial dysfunction.⁹ Although neurologic findings are relatively rare in L-HES, most of what is known about this diagnosis is extrapolated from adult patients, so the incidence of neurologic findings in pediatric L-HES is unknown. As such, the risk of recurrent stroke in our patient is unclear. He continues to follow with neurology, who have elected to continue daily aspirin for at least 1 year but are considering extending aspirin therapy for as long as he is on mepolizumab.

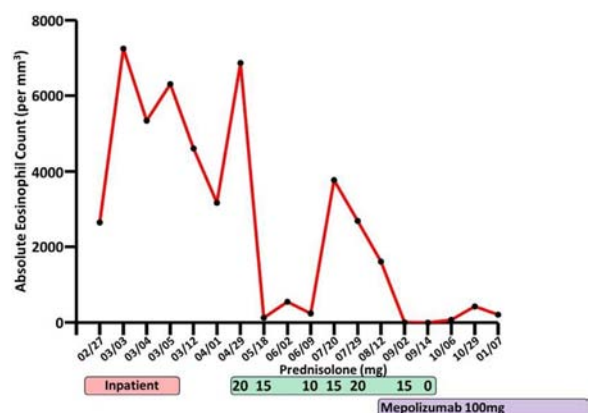


Figure 1. AECs and the effects of treatment. AECs are demonstrated over a time period of approximately 1 year, starting with the initial hospital admission. Medications and doses are aligned with the time point when they were prescribed. X-axis is labeled with mo/d. AEC, absolute eosinophil count.

Overall, this case illustrates that our newer biologics, often reserved for refractory disease, can be extended to our youngest patients in whom traditional therapies may not be ideal. For pediatric L-HES in particular, which is mediated by excessive interleukin-5 production by clonal T cells, we would advocate for early use of mepolizumab owing to its direct antagonism of the mechanism of disease and its favorable safety profile, with a goal to reduce steroid dosing to the lowest possible, if not zero, to maintain normal eosinophil counts and prevent end-organ dysfunction.

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Increased health care use in patients with moderate-to-severe asthma due to frequent preferred medication changes



Asthma is the most common chronic pediatric respiratory disease, affecting 6.1 million US children under the age of 18 years,¹ with 60% of these children diagnosed with having persistent asthma. Per guidelines of the National Heart, Lung, and Blood Institute, children with moderate and severe asthma (steps 3–6) should be prescribed daily inhaled corticosteroids (ICSs).² Studies looking at asthma hospitalizations reveal that a history of hospitalization within the past 12 months is a predictor for readmission.³ Therefore, identifying methods to provide the best asthma control possible and to eliminate barriers to care is important. Potential barriers are numerous and include the inability to access care and a lack of insurance coverage.^{4,5} Guidelines for treatment of difficult-to-control asthma have focused on re-education, assessment of barriers to care, and treatment adherence. Adherence is also influenced by multiple factors, including education, health literacy, transportation, and financial barriers.⁴ In 2016 and 2017, we observed that insurance companies in Indiana were changing their preferred ICS ± long-acting β-agonist (LABA) every 2 to 3 months. We were concerned that this was leading to gaps in medication adherence as physicians, pharmacies, and patients worked to comply with the frequent changes. Therefore, we investigated whether these frequent changes resulted in an increase in hospitalizations for asthma exacerbations within our high-risk asthma population.

Between January 2016 and December 2017, 98 children (median age 9.7 years, 60% male, 70% African American) in our high-risk asthma clinic had at least 1 hospitalization for an asthma exacerbation, for a total of 203 hospitalizations. Of the patients, 89 of 98 (91%) were covered by Medicaid administered by the state or by 1 of 4 co-

managed Medicaid-based organizations. All patients had a diagnosis of moderate or severe asthma per the guidelines of the National Heart, Lung, and Blood Institute² and were followed in the high-risk asthma clinic and prescribed daily ICS ± LABA. For each patient, medication refill history and insurance coverage were reviewed for 3 months before each hospitalization by using state refill databases and calling pharmacies. Because all patients had insurance that requires monthly refills, hospitalizations associated with one of the following were labeled noncompliant: 1) less than 2 refills of ICS in the prior 3 months, or 2) physician documentation of not taking medication as prescribed despite continuous ICS ± LABA access. Hospitalizations associated with a change in the preferred ICS ± LABA covered by that patient's insurance company within 3 months of the hospitalization and led to authorization-related delay and medication use lapse were labeled "medication refill issue." Hospitalizations associated with 2 refills in the 3 months before hospitalization and no insurance changes were labeled as compliant. Data were analyzed using Wilcoxon nonparametric test.

Most hospitalizations were associated with medication compliance with the preferred ICS ± LABA in the 3 months before hospitalization at 99 of 203 patients (49%), followed by medication noncompliance (36%) for 3 months before hospitalization, and insurance changes in the preferred ICS ± LABA in the 3 months before hospitalization (15%).

First, we compared patients based on medication compliance during the 2-year study. Half of the patients hospitalized (49 of 98) had at least 1 hospitalization associated with medication noncompliance. Compared with patients who were always compliant with medications for the 3 months before their hospital admission(s), patients with a history of at least 1 hospitalization associated with medication noncompliance had more hospitalizations during the 2-year study (noncompliant: median 2 hospitalizations [interquartile range: 1–6], compliant: 1 [1–7], $P = .002$). To evaluate whether a history of

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