

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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References

1. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med*. 2008;358(12):1215–1228.
2. Armoni Domany K, Shiran SI, Adir D, Lavie M, Levin D, Diamant N, et al. The effect of mepolizumab on the lungs in a boy with hypereosinophilic syndrome. *Am J Respir Crit Care Med*. 2020;202(2):e34–e35.
3. Schwarz C, Müller T, Lau S, Parasher K, Staab D, Wahn U. Mepolizumab—a novel option for the treatment of hypereosinophilic syndrome in childhood. *Pediatr Allergy Immunol*. 2018;29(1):28–33.
4. van Grotel M, de Hoog M, de Krijger RR, Beverloo HB, van den Heuvel-Eibrink MM. Hypereosinophilic syndrome in children. *Leuk Res*. 2012;36(10):1249–1254.
5. Arceri T, Kurland G, Reyes-Múgica M, Larkin A. Pediatric eosinophilic bronchiolitis successfully treated with mepolizumab. *J Allergy Clin Immunol Pract*. 2022;10(3):874–875.
6. Otani IM, Anilkumar AA, Newbury RO, Bhagat M, Beppu LY, Dohil R, et al. Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2013;131(6):1576–1582.
7. Burris D, Rosenberg CE, Schwartz JT, Zhang Y, Eby MD, Abonia JP, et al. Pediatric hypereosinophilia: characteristics, clinical manifestations, and diagnoses. *J Allergy Clin Immunol Pract*. 2019;7(8):2750–2758. e2.
8. Khwaja GA, Duggal A, Kulkarni A, Choudhary N, Gupta M, Chowdhury D, et al. Hypereosinophilia—an unusual cause of multiple embolic strokes and multi-organ dysfunction. *J Clin Diagn Res*. 2013;7(10):2316–2318.
9. Venkatakrishnan S, Gupta A, Khanna M, Nagappa M, Ross C. Hypereosinophilia as a cause of recurrent stroke. *Ann Indian Acad Neurol*. 2020;23(1):118–119.

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

Disclosures: The authors have no conflicts of interest to report.

Funding: This work is funded by the National Institute of Allergy and Infectious Diseases K23 career development award 1 K23 AI135094-01 and the National Institute for Health Loan Repayment Program L40 AI096442.

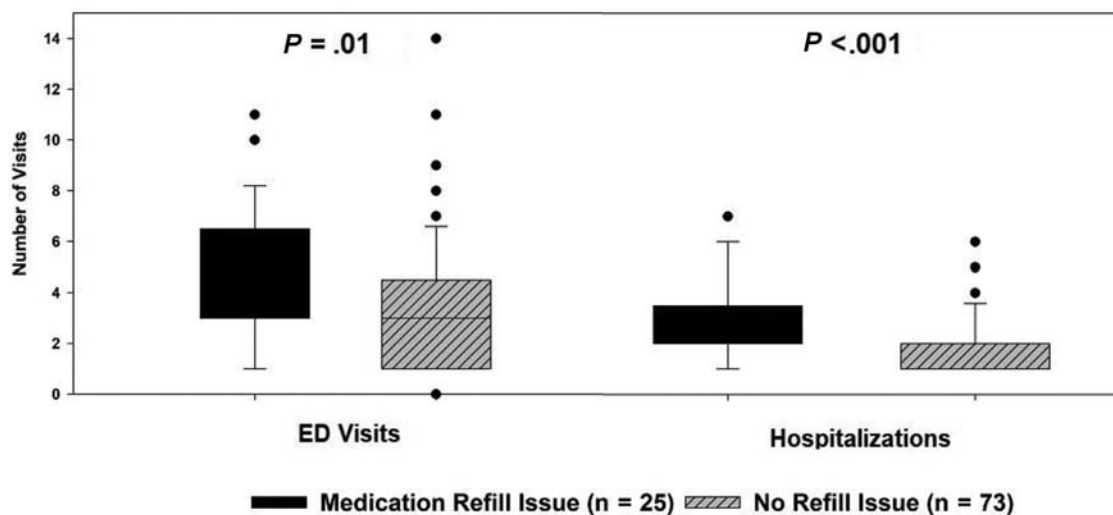


Figure 1. Patients with a “medication refill issue” had increased hospitalizations (refill issue: 2 [1–7] hospitalizations/y, no refill issue: 1 [1–6] hospitalizations/y, $P < .001$) and more ED visits (5 [1–11] visits/y vs no refill issue: 3 [0–14] visits/y, $P = .01$). ED, emergency department.

noncompliance led to an increase in emergency department (ED) visits for asthma exacerbations, we compared them with patients who never had a hospitalization associated with medication noncompliance. There was not an increase in ED visits for asthma exacerbations among those who had a history of noncompliance (noncompliant: 4 ED visits [0–14], compliant: 3 [0–9], $P = .37$).

Next, we evaluated whether medication refill issues led to an increase in hospitalizations. During the 2 years of the study, 25 of 98 patients experienced a change in the medication covered by their insurance within 3 months of their hospitalization. Compared with patients who did not experience a change in medication during the 2 years of the study ($n = 73$), those with a medication refill issue had higher rates of hospitalizations (refill issue: median 2 hospitalizations [interquartile range: 1–7], no refill issue: 1 [1–6], $P = .001$). To evaluate whether a change in preferred medication led to an increase in ED visits for asthma exacerbations, we compared ED visits for asthma during the 2-year period. Compared with patients who never experienced a refill issue during the 2 years of the study, ED visits were higher for patients who had experienced a medication refill issue during the 2-year study (experienced refill issue: median 5 ED visits [interquartile range: 1–11], never experienced a refill issue: 3 [0–14], $P = .01$) (Fig 1).

Asthma control is easier to achieve when medication is readily available and used as prescribed. Children with moderate-to-severe asthma who miss multiple ICS doses can quickly escalate to requiring emergency care. Increased hospitalizations and ED visits have been reported in children with poorly controlled asthma, and ED visits for asthma have long been used as an adverse outcome for studies of effectiveness of different asthma control therapies and practices.⁶ However, within this population, there are multiple factors that contribute to disease morbidity, including gaps in insurance coverage and access to affordable medications.^{5,7} In this retrospective chart review of patients with moderate-to-severe asthma followed in a high-risk asthma clinic, 15% of hospitalizations were associated with frequent changes in the preferred ICS $\pm$ LABA approved by insurance suggesting that frequent changes in asthma medication coverage lead to an increase in asthma exacerbations requiring higher levels of care. Noncompliant patients had more hospitalizations with no change in ED visits, suggesting that patients who are noncompliant have more severe exacerbations necessitating higher levels of care that cannot be bridged by an ED visit.

This study has several potential limitations. In determining medication compliance and refill issues, we were limited to what was reported in documentation, pharmacy refill history, and insurance

denial of medications. However, our severe asthma clinic has a full-time nurse who reviews medication refills before each clinic visit. This allows us to identify issues with medication adherence or insurance coverage with the patient during their visit. Because most clinics do not have this level of staff support, we suspect that frequent changes in preferred ICS $\pm$ LABA are another factor that contributes to asthma disparities. Another limitation is our lack of a comparison arm of patients who had a change in their preferred medication but no lapse in therapy. Of the 203 hospitalizations, only 1 was associated with a change in preferred medication with no lapse in therapy. Unfortunately, we did not capture short-acting β -agonist (SABA) use in our patients. Future studies should include this measurement to help evaluate whether failure to obtain ICS $\pm$ LABA in a timely manner leads to increased use of SABA to maintain control. It is possible that patients are labeled as uncontrolled with subsequent prescribing of higher than necessary doses of ICS when in fact patients are not able to get the lower dose of ICS filled. This study was performed before the implementation of single maintenance and reliever therapy.² It is possible that using single maintenance and reliever therapy may lead to better asthma control even in patients who encounter frequent changes in their preferred ICS $\pm$ LABA. Future studies should evaluate whether frequent changes in ICS coverage lead to (1) use of stronger medications, (2) subsequent poor compliance owing to difficulty in obtaining the correct medication, (3) an increase in SABA use, and (4) education-related barriers owing to change in color, appearance, and technique of inhaled medications.

Although causes of poorly controlled asthma are multifactorial, there are still barriers to medication use that need to be further studied. This study reveals that frequent changes in ICS coverage are associated with an increase in health care use. Our data should encourage insurance companies and pharmaceutical companies to investigate whether frequent changes in medication coverage are truly cost-effective.

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References

1. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breyse PN. Vital signs: asthma in children - United States, 2001–2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(5):149–155.
2. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPCC) Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T. 2020 Focused updates to the asthma management

guidelines: a report from the national Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217–1270.

3. Reznik M, Hailpern SM, Ozuah PO. Predictors of early hospital readmission for asthma among inner-city children. *J Asthma*. 2006;43(1):37–40.
4. Shields AE. Trends in private insurance, Medicaid/State Children's Health Insurance Program, and the health-care safety net: implications for asthma disparities. *Chest*. 2007;132(5 Suppl):818S–830S.
5. Gushue C, Miller R, Sheikh S, Allen ED, Tobias JD, Hayes Jr D, et al. Gaps in health insurance coverage and emergency department use among children with asthma. *J Asthma*. 2019;56(10):1070–1078.
6. Cloutier MM, Hall CB, Wakefield DB, Bailit H. Use of asthma guidelines by primary care providers to reduce hospitalizations and emergency department visits in poor, minority, urban children. *J Pediatr*. 2005;146(5):591–597.
7. Pate CA, Qin X, Bailey CM, Zahran HS. Cost barriers to asthma care by health insurance type among children with asthma. *J Asthma*. 2020;57(10):1103–1109.

Effect of immune checkpoint inhibitors on asthma



Anticancer strategies using immune checkpoint inhibitors (CPIs) are increasingly being used. The most common strategies involve monoclonal antibodies targeting cytotoxic T lymphocyte associated antigen-4, programmed cell death protein (PD-1), and programmed cell death ligand 1.¹ By blocking the natural regulation of T cells, they activate cytotoxic T cells and shift the immune system toward antitumor activity. In some patients, adverse events have been seen with these therapies.¹ Mechanistically, it has been suggested that immune-related adverse events (irAE) may be linked to an autoimmune process secondary to T-cell receptor inhibitory phosphatases that maintain tolerance to autoantigens.²

Pneumonitis has been described as a rare but potentially life-threatening irAE, with a frequency of 5% in patients treated with anti-PD-1 or programmed cell death ligand 1 therapy.² However, exacerbations of preexisting lung conditions have not been ascertained. The study by Galant-Swofford et al³ reported that pneumonitis occurred more frequently in patients with a history of asthma and chronic obstructive pulmonary disease than in those without this history. Despite this, to the best of our knowledge, there have not been any other studies that support this finding.³ Asthma is characterized by the increased presence of T helper 2 cell lymphocytes and eosinophils.³ A recent case report study has described asthma as an irAE in a patient aged 70 years, diagnosed with unresectable bladder cancer on anti-PD-1 therapy.^{4,5} Because of this case study, and the fact that CPIs have been documented to increase eosinophil levels,⁶ we were interested in the relationship between CPIs and asthma, specifically whether CPIs worsen underlying asthma.

Our study is a collaborative project between Memorial Sloan Kettering Cancer Center in New York and National Jewish Health in Denver. As of January 5, 2022, we enrolled 83 patients with grade 2 or higher immune-related cutaneous adverse events (ircAE) and 32 subjects in our comparison group: those on CPIs without any ircAEs. Based on a self-reported atopic diseases questionnaire, 13 patients in

the study have reported a history of asthma. Six of these patients had pruritus without rash; 3 had eczema; 1 had a maculopapular rash; and 3 had no cutaneous adverse events.

Of the 13 patients with a history of asthma, most were White men (11 of 13 White, 9 of 13 male) with an average age of 65 years (ranging from 41 to 87 years old). Four were treated for kidney cancer, 2 for bladder cancer, 2 for thyroid cancer, 1 for prostate cancer, 1 for pancreatic cancer, 1 for endometrium cancer, 1 for liver cancer, and 1 for melanoma. Four had no asthma medications listed; 4 of them were on inhaled corticosteroids (ICS) with short acting bronchodilators as rescue (2 with leukotriene inhibitor as well); 2 were on inhaled corticosteroids and a long-acting bronchodilator (ICS-LABA) with a short acting beta agonist (SABA) as rescue; 1 was on SABA only; 1 was on an oral leukotriene inhibitor only; and 1 was on SABA and an oral leukotriene inhibitor. With the introduction of a CPI, 1 patient had 5 mg prednisone added to their asthma regimen (changing from ICS + SABA + leukotriene inhibitor to ICS + SABA + leukotriene inhibitor + 5 mg prednisone), and another had a leukotriene inhibitor added (ICS + SABA + montelukast). The remaining 11 patients had no change in asthma medications after starting CPIs, including those with no asthma medication listed, even though 9 of 11 of those patients had an increase in eosinophil levels with the increase ranging from 1.4 to $11 \times 10^9/L$; $P = .05$). Thus, although lung adverse events, like pneumonitis, can be induced with CPI use, we found no evidence for exacerbation of asthma in our patient population.

Acknowledgment

The authors acknowledge Nicole Meiklejohn for her assistance in preparing this manuscript.

Disclosures: Dr Lacouture has a consultant role with Johnson and Johnson, Novocure, QED, Bicara, Janssen, Novartis, F. Hoffmann-La Roche AG, EMD Serono, Astrazeneca, Inovovaderm, Deciphera, DFB, Azitra, Kintara, RBC/La Roche Posay, Trifecta, Varsona, Genentech, Loxo, Seattle Genetics, Lutris, OnQuality, Azitra, Roche, Oncoderm, NCODA, and Apricity. Dr Lacouture also receives research funding from Lutris, Paxman, Novocure, J&J, US Biotest, OQL, Novartis, and AZ, and is funded in part through the National Institutes of Health/National Cancer Institute (NIH/NCI) Cancer Center Support Grant P30 CA008748. The remaining authors have no conflicts of interest to report.

Funding: Edelstein Family Chair of Pediatric Allergy-Immunology, the Eugene F. and Easton M. Crawford Charitable Lead Unitrust, NIH/NCI Cancer Center Support Grant P30 CA008748. Dr Kraehenbuehl is also supported by the Swiss National Science Foundation.

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