can have many causes.[6] Many studies of pediatric patients referred for consultation for EID showed EIB in only 8% to 19%, in line with our findings.[1-3] Although most of our patients had been prescribed bronchodilators for suspected EIB, only 10% showed EIB on CPET results. This highlights that self-reported exercise-induced symptoms are poor predictors of EIB. Therefore, other causes of EID should be considered, especially in patients with no significant clinical response to bronchodilators.

Vocal cord dysfunction is characterized by paradoxical closure of vocal cords during inspiration, causing stridor and dyspnea. In our study, VCD was the most common primary cause of EID (27%). In 294 pediatric patients with EID, Hseu et al[7] also found VCD as the most frequent cause (30%) of exercise intolerance.[7] The incidence tends to be higher in female athletes.[8] We did not see any dependence between sex and VCD in our cohort. The documentation of excessive respiratory rate or an abnormal drop in CO_2 during exercise with a consistent history is often diagnostic of EIH.[5] In a study done in pediatric patients with atypical or refractory asthma, one third of these patients demonstrate EIH.[9] Abnormal ventilatory homeostasis during exercise could be the underlying reason.[9] We saw evidence of EIH in 10% of our patients, and it was approximately 6 times more common in females. Progesterone combines with estrogen to increase ventilation by action both centrally and on the carotid body, which explains the higher prevalence in females.[10]

Physiological limitation, often a diagnosis of exclusion, is related to an excessive sensation of the perceived work of breathing with increased ventilation. In a study done by Abu-Hasan et al[1] on 142 children and adolescents with EID, the most common cause was a normal physiological limitation (52%).[1] Physiological limitation as a cause of EID was the second most frequent cause in our study group. Seear et al[2] showed that 23% of those previously diagnosed with EIB were considered "unfit" (deconditioned) based on CPET, in contrast to 10% in this study.[2] Deconditioned subjects accumulate lactate at a lower level of exercise, with resultant increased metabolic acidosis and ventilation.[4] Eleven percent of our patients had obesity as the primary contributor to EID because of excessive metabolic requirement and ventilatory limitation.[4] Pulmonary limitation is a rare cause of EID in apparently well individuals. Eleven percent of patients in the series published by Abu-Hasan et al[1] had chest wall restriction (attributable to mild pectus deformity or scoliosis) as a cause of EID.[1] In our cohort, 5% showed abnormal cardiac or pulmonary limitation, including mainly patients with chest wall abnormalities (pectus excavatum, scoliosis).

In conclusion, CPET was helpful in assessing pediatric EID patients who failed to improve after routine interventions. Exercise-induced bronchospasm was present in few patients, and most of the patients had other causes of EID. Based on these results, we were able to provide specific recommendations to our patients. Although it is expensive and more complex, CPET should be considered in pediatric EID patients, especially in patients with an absence of significant response to asthma treatment.

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Poor control of asthma symptoms with interleukin-5 inhibitors in four patients with aspirin-exacerbated respiratory disease

Check for updates

Aspirin-exacerbated respiratory disease (AERD) is a condition of the respiratory tract characterized by rhinosinusitis, asthma, eosinophilia, and respiratory reactions to nonsteroidal anti-inflammatory drugs. The pathophysiology of AERD involves a baseline dysregulation of arachidonic acid metabolism leading to the overproduction of leukotrienes.[1] Leukotrienes are inducers of bronchoconstriction and also attract eosinophils into the airways.[2] The overproduction of leukotrienes in AERD is further exacerbated by cyclooxygenase-1 inhibitors.[1] Paradoxically, aspirin desensitization improves respiratory symptoms in 67% to 78% of patients.[3] However, additional treatments are needed because some patients who fail to improve cannot tolerate aspirin.[3,4]

The respiratory tract in AERD is characterized by eosinophilic infiltration, with nasal polyps and bronchial biopsies demonstrating more eosinophils and higher levels of interleukin-5 (IL-5) than in patients with aspirin-tolerant-asthma.[5,6] Interleukin-5 is an eosinophilic maturation and differentiation factor contributing to tissue and peripheral eosinophilia.[7] These characteristics suggest

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Table 1
Characteristics of the 4 Patients at the Time of Treatment with Mepolizumab and Follow-up Eosinophil Counts

Characteristic	Case 1	Case 2	Case 3	Case 4
Sex	Female	Female	Female	Male
Age (y)	30	52	68	33
Race	White	AA	AA	AA
BMI	50	40	30	38
Lifetime sinus polypectomy	2	3	3	3
Medications	Aspirin 650 mg twice per day Fluticasone/salmeterol 500/50 μg twice per day Montelukast 10 mg once per day Albuterol as needed	Aspirin 650 mg twice per day Fluticasone/vilanterol200/25 μg twice per day Montelukast 10 mg Daily Albuterol as needed	Fluticasone/vilanterol 500/50 μg twice per day Albuterol as needed	Mometasone/formoterol 200/5 μg twice per day Omalizumab 300 mg every 4 weeks Albuterol as needed
Oral steroid use[a]	7 prednisone tapers in 12 months before initiation with mepolizumab	Prednisone 20 mg daily with 4 prednisone tapers 12 months before mepolizumab	8 prednisone tapers in 12 months before mepolizumab	Prednisone 20mg daily with 6 prednisone tapers 12 months before mepolizumab
Blood eosinophil count before mepolizumab (cells/μL)	2800	800	1600	2100
FEV_1 (% predicted)	81%	62%	67%	34%
Blood eosinophil count nadir on mepolizumab (cells/μL)	200	0	100	0
Blood eosinophil count peak on mepolizumab (cells/μL)/ number of months until peak AEC and discontinuation of mepolizumab	600 / 8 months	300 / 3 months	300 / 14 months	400 / 7 months
Months until first steroids taper	3	2	5	4
Total number of steroid tapers on mepolizumab	6	1	3	8
Course after mepolizumab failure	Switched to reslizumab, then 7 prednisone tapers	Switched to dupilumab then was lost to follow-up as she moved away from the area	Switched to benralizumab then 4 prednisone tapers in 6 months, applied for dupilumab at the time of manuscript	Switched to benralizumab, then had 2 prednisone tapers in 4 months, while continuing hydrocortisone daily, applied for dupilumab at the time of manuscript
Blood eosinophil count nadir on alternative biologic (cells/μL)	100	0	0	100

Abbreviations: AA, African America; BMI, body mass index; FEV_1, forced expiratory volume in 1 second.
[a]Prednisone tapers prescribed to these patients were starting at 40 mg, lowering the dose by 10 mg every 3 days, finishing with 5 mg for 3 days, for a total of 15 days.

that patients with AERD should benefit from therapies that target eosinophilic inflammation.

Mepolizumab, a monocolonal antibody against IL-5, has been shown to decrease asthma exacerbations and blood eosinophilia in patients with asthma.[8] Although IL-5 antagonists are of interest in AERD, data on anti–IL-5 treatment in this group are scarce. Only 1 study has explored the role of mepolizumab in AERD and described improvement of asthma, nasal symptoms, and peripheral absolute eosinophil count (AEC) during the first several months of treatment.[9] We describe 4 patients with AERD who were treated with mepolizumab for severe glucocorticoid-dependent asthma and who experienced poor asthma control and elevation of AEC months after treatment.

Subjects at Brigham and Women's Hospital AERD Center and Montefiore Hospital AERD Center who received mepolizumab for at least 2 months were included. The AERD diagnosis was confirmed by aspirin challenge in all patients. This retrospective study was approved by the Partners health care and Montefiore Institutional Review Board. Data were extracted from Partners Healthcare and Montefiore electronic medical record (Epic Systems, Verona, WI). Data reported are means ± standard deviation.

Of the 4 subjects with AERD, 2 (50%) were maintained on aspirin for AERD, whereas the others could not tolerate aspirin because of side effects. Three (75%) were female, 3 identified as African American (AA), and all were obese. The average age was 46.8 ± 7.7 years. At baseline, AEC ranged from 800 cells/μL to 2800 cells/μL. Average peripheral AEC was 1800 cells/μL, and all had poorly controlled glucocorticoid-dependent asthma, with 2 (50%) requiring daily oral corticosteroids and 2 (50%) requiring 6 or more oral corticosteroid bursts per year before mepolizumab. The average number of lifetime polypectomies was 2.75 ± 5, and the average forced expiratory volume in 1 second (FEV_1) before mepolizumab was 61 ± 19.7. Mepolizumab was initiated with an oral glucocorticoid burst. Before starting mepolizumab, all patients were not receiving other biologics. Subject 4 had been on omalizumab, which was discontinued 20 months before mepolizumab because of the lack of effectiveness. All patients were treated with standard mepolizumab dosage for asthma at 100 mg subcutaneously every 4 weeks and initially had a decrease in AEC and did not require additional steroids (Table 1).

Despite compliance with mepolizumab, all patients developed an increase in AEC, with concomitant asthma exacerbations requiring oral glucocorticoids after 3.5 ± 1.3 months of treatment. Sputum eosinophilia and sinonasal symptoms were not evaluated in these patients. Patients were treated with mepolizumab for 8.0 ± 4.5 months before discontinuation of mepolizumab. All subjects were trialed on alternative biologics but continued to have poor asthma control requiring courses of oral glucocorticoids.

Our study identifies a subset of AERD patients who failed to have a prolonged response to mepolizumab despite an initial decrease in AEC. All subjects developed asthma exacerbations requiring steroids after months of treatment. Only one other study, by Tuttle and

colleagues,[9] has examined the efficacy of mepolizumab in AERD. Our findings contradict those by Tuttle and coworkers despite the similarity of the subjects. Both studies comprised overweight women with a similar number of lifetime polypectomies (2.75 vs 2.5) and similar FEV_1% predicted before starting mepolizumab (61 ± 19.7 vs 63.5 ± 24.2). In addition, 50% of subjects in both studies were receiving daily oral glucocorticoids. Subjects in our study were younger (46.8 ± 17.7 vs 54 ± 14.8), had a higher average AEC before starting mepolizumab (1800 vs 842), and were mostly AA. Racial demographic data were not included in the study by Tuttle et al. Although the focus of Tuttle and colleagues was on the sinonasal symptoms in AERD, they found that subjects with AERD treated with mepolizumab had decreased AEC without the need for increased oral glucocorticoids.[9] At the time of data collection, subjects had been on mepolizumab for an average of 5.5 months.

In contrast, subjects in our studies required oral glucocorticoids months after initiation of mepolizumab. Subjects required multiple courses of oral glucocorticoids and continued to have asthma exacerbations and increases in AEC. All subjects discontinued mepolizumab months after stating the medication. At the time of data collection, subjects had been on mepolizumab for an average of 8 months.

This report has its limitations. It involves a small number of subjects with AERD. In our study, mepolizumab was initiated together with a steroid burst, making less clear whether the initial reduction in AEC was attributable to mepolizumab alone. In addition, sputum eosinophilia was not measured in these patients.

Nevertheless, our findings are relevant because sparse data exist from clinical practice on the effect of anti–interleukin (IL)-5 pathway biologics in AERD, and our findings challenge the conclusion of the only study exploring mepolizumab in AERD. One reason why our findings are different may be the demographics of our subjects. Aspirin desensitization in minority populations have been found to be less successful than in whites.[10] Possibly minority patients may have a poor response to mepolizumab. Further studies are needed to explore this phenomenon. Finally, all subjects underwent trials on alternative biologics but continued to have poor asthma control that required glucocorticoids. As biologics become common in clinical practice, clinicians must recognize the limitations of these medications. Future studies are needed to explore the efficacy of mepolizumab and other biologics in patients with AERD.

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Drug hypersensitivity testing

Baboon syndrome precipitated by amoxicillin challenge

Check for updates

Although beta-lactam “allergy” may be self-reported in up to 10% of individuals, only a minority of these individuals (3%-5%) will have genuine type 1 immunoglobulin E (IgE)-mediated hypersensitivity.[1]

Because an increasing trend has been found amongst health care professionals for penicillin delabeling, potential sequelae of this approach should be considered. We report the first case of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) after oral amoxicillin challenge.

A 19-year-old woman was referred for investigation of possible penicillin allergy, based on a childhood history of rash developing after amoxicillin treatment. Details of the rash onset, distribution, and resolution were not available. She had no systemic symptoms suggestive of type 1 IgE-mediated hypersensitivity. Her medical history included hypothyroidism and aplastic anaemia, for which she underwent matched unrelated donor bone marrow transplantation (aged 3). Drug history comprised thyroxine and erythromycin as antibiotic prophylaxis posttransplantation. Skin prick testing and blood measurement for specific IgE to the major determinants of penicillin (penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl) and cefaclor was negative (Phadia 2500, Thermo Fisher Scientific United Kingdom). To exclude penicillin allergy, a

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