Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

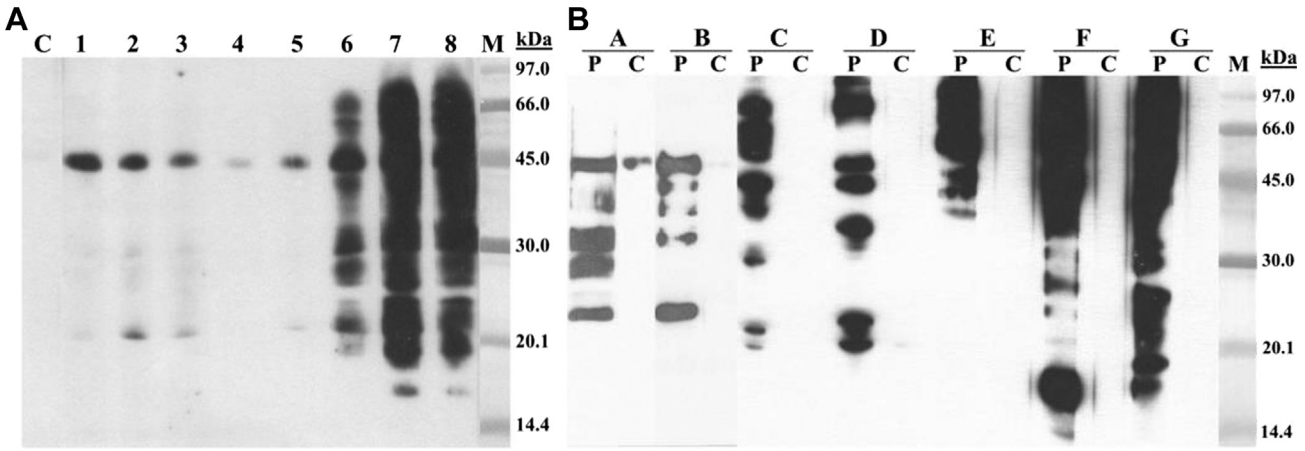

Figure 1. A, SDS-PAGE immunoblotting results. Includes (A) star fruit pulp extract, (B) star fruit seed extract, (C) seed-1 extract, (D) seed-2 extract, (E) seed- 3 extract, (F) wheat seed extract, and (G) corn seed extract. kDa, kilodalton; M, molecular mass marker; SDS-PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis. **B**, SDS-PAGE immunoblotting inhibition results. The solid phase is star fruit (pulp). Lane C is the control serum (pooled of sera from patients who were nonatopic). Lane 1 is the patient serum preincubated with an extract from type seed-1 (bird food). Lane 2 is the patient serum preincubated with an extract from type seed-2 (bird food). Lane 3 is the patient serum preincubated with an extract from type seed-3 (bird food). Lane 4 is the patient serum preincubated with an extract from wheat seed. Lane 5 is the patient serum preincubated with extract corn seed. Lane 6 is the patient serum preincubated with bromelain. Lane 7 is the patient serum preincubated with ovalbumin. Lane 8 is the patient serum preincubated with lamb extract.

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References

1. Silva KDRR, Sirasa MSF. Antioxidant properties of selected fruit cultivars grown in Sri Lanka. *Food Chem*. 2018;238:203–208.
2. Neto MM, Silva GEB, Costa RS, et al. Star fruit: simultaneous neurotoxic and nephrotoxic effects in people with previously normal renal function. *NDT Plus*. 2009;2(6):485–488.
3. Aranguren C, Vergara C, Rosselli D. Toxicity of star fruit (*Averrhoa carambola*) in renal patients: a systematic review of the literature. *Saudi J Kidney Dis Transpl*. 2017;28(4):709–715.
4. Herbland A, El Zein I, Valentino R, et al. Star fruit poisoning is potentially life-threatening in patients with moderate chronic renal failure. *Intensive Care Med*. 2009;35(8):1459–1463.
5. Tsai MH, Chang WN, Lui CC, et al. Status epilepticus induced by star fruit intoxication in patients with chronic renal disease. *Seizure*. 2005;14(7):521–525.
6. Numata T, Ito T, Egusa C, Kobayashi Y, Maeda T, Tsuboi R. A case of oral allergy syndrome due to star fruit sensitized from atopic hands. *Allergol Int*. 2015;64(4):393–395.

Severe acute respiratory syndrome coronavirus 2 infection in those on mepolizumab therapy

Check for updates

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] continues to cause morbidity and mortality across the world. The expert recommendation is to continue biologic therapy unchanged in severe eosinophilic asthma[2,3] but concern has been expressed as eosinopenia may be a risk factor for worse disease outcomes.[4,5] Here, we report the outcomes of 4 patients from centers in the United Kingdom, Italy, and North America with COVID-19, while receiving treatment with mepolizumab, an anti–interleukin 5 monoclonal antibody, which reduces eosinophils to within the reference range.[6]

Case 1 is a 64-year-old White man with a history of childhood-onset asthma, atopy, and rhinitis, whose asthma control deteriorated in his mid-40s. Despite treatment with high-dose inhaled corticosteroids (ICS), long-acting β-agonist (LABA), leukotriene receptor antagonist (LTRA), macrolides, and intranasal steroids, his disease remained poorly controlled with an asthma control questionnaire 6 (ACQ-6) score of 3.1, regular exacerbations, marked airflow limitation (forced expiratory volume in 1 second [FEV1] of 44%) and blood eosinophil count of at least 500 cells/μL. Mepolizumab was started in 2013 with a consequent reduction in eosinophil counts (200 cells/μL) and exacerbations (4 to 1 per year). In March 2020, he presented to the emergency department after 10 days of fever, dyspnea, cough, and central pleuritic chest pain. He had mild wheeze on auscultation, reduced peak expiratory flow (130, normally 250) but was apyrexial, and a chest radiograph (CXR) found no radiological evidence of pulmonary infiltrates. Blood test results revealed eosinopenia (0 cells/μL), elevated C-reactive protein (147 mg/L), and SARS-COV-2 was confirmed by polymerase chain reaction (PCR). He was treated for asthma exacerbation and discharged home. After 2 weeks, he still felt fatigued, but his respiratory symptoms had otherwise settled.

Case 2 is a 61-year-old White man with late-onset asthma, chronic sinusitis, nasal polyposis, and bronchiectasis with gastroesophageal reflux disease, obstructive sleep apnea, hypertension, and hypercholesterolemia. Despite treatment with high-dose ICS, LABA and LTRA

Disclosures: Dr Howarth reports employment by GlaxoSmithKline. The remaining authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

therapy, he had poor disease control with an ACQ-5 score of 2.83 and regular exacerbations. He was sensitized to house dust mite, had marked airflow limitation (FEV1 64%), and raised blood eosinophil counts greater than 900 cells/μL. He was started on mepolizumab in 2019 and, in parallel to a reduction in blood eosinophils (to 70 cells/μL), saw improvement in his FEV1 (increased by 450 mL), reduction in exacerbations, and improvement in ACQ-5. In March 2020, he presented to the emergency department in acute respiratory failure after 5 days of fever, breathlessness, cough, chest tightness, and anosmia. Admission investigations revealed new unilateral CXR changes and blood eosinopenia (0 cells/μL), and real-time PCR was positive for SARS-COV-2. He was admitted for treatment with supplementary oxygen, ceftriaxone, azithromycin, dexamethasone, and intermediate-dose enoxaparin. He required continuous positive airway pressure ventilatory support and was given tocilizumab due to clinical suspicion of COVID-19-related cytokine storm. The patient was discharged home after 13 days and, after a period of convalescence at home, reported resolution of his respiratory symptoms.

xCase 3 is a 66-year-old White woman with childhood-onset asthma and chronic rhino-conjunctivitis, 15 pack-year smoking history, and history of using biomass heating. Her comorbidities included type 2 diabetes (requiring insulin), myocardial infarction, and gastroesophageal reflux disease. Spirometry measured an FEV1 of 500ml (29% predicted) with an FEV1-to-forced vital capacity of 47%; she required overnight and ambulatory (2 L/min) oxygen therapy and was treated with high-dose inhaled ICS, LABA, long-acting muscarinic antagonist, and LTRA therapy. In view of her recurrent exacerbations and elevated blood eosinophil counts (440 cells/μL), she was given methylprednisolone 20 mg/day (intolerant of other oral corticosteroids) before starting mepolizumab in September 2019. At 6 months, blood eosinophil counts had reduced (to 0 cells/μL) as had ACQ-5 (from 3.67 to 1); methylprednisolone was discontinued, although she continued to exacerbate. In March 2020, she presented to the emergency department with a 2-day history of fever, dyspnea, and epigastric pain. Clinical examination and CXR were unremarkable, but real-time PCR was positive for SARS-COV-2. She was discharged home to self-isolate and 3 weeks later, repeat nasopharyngeal swabs were negative, and dyspnea had improved, although fatigue and sporadic episodes of chest tightness persisted.

Case 4 is a 22-year-old African American woman who suffered multiple episodes of extensive deep vein thrombosis, pulmonary emboli, and interatrial clots associated with an elevated lupus anticoagulant and poor anticoagulation compliance. The bone marrow aspirate for investigation of persistent peripheral blood eosinophilia (1700 cells/μL) exhibited no blasts. She was started on prednisolone for hypereosinophilia (hypereosinophilic syndrome) and trialed a number of steroid-sparing agents, which were discontinued owing to noncompliance and recurrent hypereosinophilia. Mepolizumab (750 mg intravenous every 4 weeks) was started in 2003 through the compassionate use program by GlaxoSmithKline. Steroids and interferon alpha were tapered off by 2015, and blood eosinophil levels have reduced to a sustained level of 200 cells/μL. However, owing to new pancytopenia associated with GATA 2 haploinsufficiency, she is currently awaiting a bone marrow transplant. In July 2020, she presented to the local emergency department with a 2-day history of headache and diffuse body ache. Clinical examination was unremarkable, as was the CXR and head computed tomography results. Her blood eosinophil count was 100 cells/μL, PCR was positive for SARS-COV-2, and the patient was discharged home to self-isolate. Two weeks later, she reported a complete resolution of all symptoms.

Here, we report COVID-19 outcomes for 4 patients receiving mepolizumab therapy. At presentation with SARS-CoV-2 infection, they exhibited a further reduction in their eosinophil counts, consistent with the observation that eosinopenia may have a diagnostic use for COVID-19.[7] The mechanisms behind this observation are not fully understood[8]; there is no evidence that this represents eosinophilic infiltration of pulmonary tissue[9] and so may represent diminished eosinophil progenitor generation by other cytokines such as GM-CSF. Despite all these patients being treated with mepolizumab, only 1 patient in this series required hospitalization and ventilatory support—this patient had recognizable risk factors for admission and death in COVID-19, namely: male sex, older age, and chronic cardiac disease.[10] Nevertheless, they recovered without immediate evidence of long-term respiratory consequences, though this will need further tracking. These outcomes are in keeping with the lack of consistent evidence that patients with eosinophil-associated diseases or treatment with eosinophil-targeting therapies should have an altered outcome in COVID-19[8] and supports the position papers that biologics, such as mepolizumab, should be continued unchanged.

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References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727–733.
2. Bousquet J, Jutel M, Akdis CA, et al. ARIA-EAACI statement on asthma and COVID-19 (June 2, 2020). *Allergy*. 2020.
3. Klimek L, Pfaar O, Worm M, et al. Use of Biologicals in allergic and type-2 inflammatory diseases during the current COVID-19 pandemic: position paper of Ärzteverband Deutscher Allergologen (AeDA)[A], Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI)[B], Gesellschaft für Pädiatrische Allergologie und Umweltmedizin (GPA)[C], Österreichische Gesellschaft für Allergologie und Immunologie (ÖGAI)[D], Luxemburgische Gesellschaft für Allergologie und Immunologie (LGAI)[E], Österreichische Gesellschaft für Pneumologie (ÖGP)[F] in co-operation with the German, Austrian, and Swiss ARIA groups[G], and the European Academy of Allergy and Clinical Immunology (EAACI). [H] *Allergol Select*. 2020;4:53–68.
4. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020;75(7):1730–1741.
5. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. *Am J Respir Crit Care Med*. 2020; 201(11):1372–1379.

6. Hartl S, Breyer MK, Burghuber OC, et al. Blood eosinophil count in the general population: typical values and potential confounders. *Eur Respir J*. 2020;55(5):1901874.
7. Li Q, Ding X, Xia G, et al. Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: a retrospective case-control study. *EClinicalMedicine*. 2020;23:100375.
8. Lindsley AW, Schwartz JT, Rothenberg ME. Eosinophil responses during COVID-19 infections and coronavirus vaccination. *J Allergy Clin Immunol*. 2020;146(1):1–7.
9. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 autopsies, Oklahoma, USA. *Am J Clin Pathol*. 2020;153(6):725–733.
10. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985.

The association of trimethoprim-sulfamethoxazole with improved lung function in pediatric asthma

Asthma affects more than 300 million patients worldwide and is characterized by intermittent reversible airflow obstruction and airway inflammation. *Pneumocystis*, an opportunistic fungus, has recently been implicated in asthma pathogenesis. In preclinical models, *Pneumocystis* exposure causes goblet cell hyperplasia, bronchial hyperreactivity, and airway inflammation.[1,2] From a clinical perspective, patients with severe asthma have elevated anti-*Pneumocystis* antibody titers compared with healthy controls, and higher levels of anti-*Pneumocystis* immunoglobulin G are correlated with worsened lung function.[1] Furthermore, an evaluation of the lung mycobiome identified that *Pneumocystis jirovecii* 18S rRNA was more abundant in the bronchoalveolar lavage fluid of patients with severe asthma compared with controls without asthma.[3] Cumulatively, these studies suggest that *Pneumocystis* may represent an unrecognized contributor to asthma pathophysiology.

In this study, we sought to determine if *Pneumocystis* treatment improved lung function or exacerbation frequency in patients with asthma. We compared children who received trimethoprim-sulfamethoxazole (TMP-SMX), a standard therapeutic for *Pneumocystis*, with patients with asthma who received clindamycin, an antibiotic without activity against *Pneumocystis* that is commonly used for similar indications (eg, skin and soft tissue infections) as a control.[4] The electronic health record was queried for all patients from 2010 to 2018 who had an order or prescription for TMP-SMX or clindamycin and at least 1 spirometry. Each record was then manually reviewed for a diagnosis of asthma and for exclusion criteria (cystic fibrosis, ciliopathy, transplantation, malignancy, bronchiectasis, restrictive lung disease, prematurity less than 32 weeks, bronchopulmonary dysplasia, ventilator dependence, congenital heart disease, immunodeficiency, sickle cell disease, collagen vascular disorders, and one-time doses of antibiotic). This study was approved by the institutional review board (STUDY19010136).

Between 2010 and 2018, 79,047 orders of TMP-SMX and 86,033 orders of clindamycin were placed for 14,109 and 20,283 unique patients, respectively. Similarly, 46,215 spirometry procedures were performed on 16,444 unique patients. Among patients with spirometry data, there were 1089 patients with an order for TMP-SMX and 937 patients with an order for clindamycin. After chart review and exclusion, 144 patients with asthma in the TMP-SMX group and 202 patients with asthma in the clindamycin group were included in the cross-sectional analysis (Table 1, right). Of those, 24 patients in the TMP-SMX group and 41 patients in the clindamycin group had both baseline and follow-up spirometry (±12 months of antibiotic course) and were included in the longitudinal analysis (Table 1, left). Demographics between the TMP-SMX and clindamycin groups were similar, although TMP-SMX was prescribed more commonly for urologic indications (Table 1).

Baseline spirometry results revealed no differences in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, or forced expiratory flow at 25% to 75% between antibiotic groups (Table 1). Similarly, there were no significant differences in the interval between baseline spirometry to antibiotics or antibiotics to follow-up spirometry. There were no differences in the proportion of patients requiring either an escalation or de-escalation in therapy between the measurement of spirometry.

In patients who received TMP-SMX, there was a significant increase in FEV1 between baseline and follow-up spirometry ($P = .002$ by paired t test) (Table 1); in contrast, there was no significant FEV1 change in the clindamycin group ($P = .78$). Of note, 79% of patients with asthma receiving TMP-SMX had an increased FEV1 at the follow-up, compared with 44% in the clindamycin group ($P = .01$). Similarly, there was a significant increase in FVC with TMP-SMX ($P = .02$) but not clindamycin ($P = .54$). After adjusting for age, sex, race, antibiotic indication, inhaled corticosteroid dose, and the time intervals between spirometry and antibiotics, the improvements in FEV1 and FVC were again significantly higher in the TMP-SMX group than in the clindamycin group. Furthermore, patients who received TMP-SMX had a significant reduction in the proportion and the total number of emergency department visits for asthma exacerbations the 12 months after antibiotics (Table 1, right).

To our knowledge, this is the first association between the use of an antibiotic active against *Pneumocystis* and the improvement of lung function and asthma control. The role of antibiotics in asthma pathogenesis has been evaluated previously. Any antibiotic use, including TMP-SMX, within the first 6 months of life is associated with the development of atopic diseases, including asthma.[5] Therapeutically, there is limited evidence for lung function improvement after antibiotic treatment in the setting of an exacerbation.[6] As a long-term therapy used outside of exacerbations, however, macrolide antibiotics have been found to increase peak flow measurements and correlate with improved symptoms without changes in lung function measures.[7] None of these studies, however, evaluated antibiotics with activity against *Pneumocystis* or assessed changes in pulmonary function or exacerbation rate after the antibiotic course.

The only known natural reservoir of *Pneumocystis jirovecii* is humans, and near-ubiquitous *Pneumocystis* prevalence has been found in infants on autopsy specimens.[8,9] The presence of *Pneumocystis* has been associated with increased MUC5AC expression, a mucin implicated in asthma pathogenesis.[9,10] The detection of subclinical *Pneumocystis* infection or *Pneumocystis* colonization is limited by the lack of a noninvasive biomarker. Future studies characterizing the natural history of *Pneumocystis* burden in the lungs of patients with asthma could be highly informative.

There are several limitations to this study. Despite being at a large tertiary care pediatric hospital, the cohort of patients with

Disclosures: The authors have no conflicts of interest to report.
Funding Sources: This study was partly funded by grants from the US National Institutes of Health (grant numbers HL149693 and K08HL128809 to Dr Forno and Dr Campfield, respectively).