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.

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Letters

Clinical course of asthma in 4 cases of coronavirus disease 2019 infection

Since the first case of severe acute respiratory syndrome coronavirus 2 infection on January 22, 2020, the number of positive cases and deaths has rapidly increased.[1] The initial report of 140 hospitalized patients infected with coronavirus disease 2019 (COVID-19) from Wuhan, China, indicated that allergic diseases, asthma, and chronic obstructive pulmonary diseases were not risk factors for severe acute respiratory syndrome coronavirus 2 infection.[2] However, the clinical features of this condition with cough and shortness of breath (SOB) might mask, or mimic, an asthma exacerbation.[3] Given the evolving nature of this pandemic, the initial summary may not represent the clinical course of patients with asthma in other parts of the world. In this case series, we summarize the clinical course of 4 patients with asthma and COVID-19 infection presenting in the first month of the pandemic in Chicago, Illinois (Table 1). All these individuals were established patients with an academic allergy and immunology clinic and had controlled asthma at baseline.

Case 1

A 34-year-old woman with allergic rhinitis and severe persistent asthma presented to the emergency department (ED) with a 1-week history of wheezing, SOB, productive cough, new onset anosmia, myalgia, and fever with a temperature maximum of 104°F. Her peak expiratory flow rate 12 days before presentation was at baseline of 400 L/minute, and 10 days before, she was examined by her pulmonologist who documented that the patient's asthma was controlled. On day 3 of symptom presentation, she was screened through telephone, referred to a testing site, and tested for COVID-19 infection. The patient increased her use of metered-dose inhaler and nebulized albuterol without relief over the next few days. On day 6, she was feeling better. However, by day 7, her SOB worsened which prompted her to seek medical attention. In the ED, she was in hypoxemia, had sinus tachycardia (heart rate of 129 beats per minute), and was audibly wheezing. Chest X-ray examination revealed diffuse bilateral ground-glass attenuation. She was admitted and treated for pneumonia with levofloxacin for pneumonia and prednisone at a dose of 40 mg daily for asthma exacerbation. On day 8, her previous COVID-19 test result returned positive, and therefore her antibiotics were discontinued. When lying supine, her oxygen saturation decreased to 88% but improved to 94% with repositioning and albuterol treatment. She continued to have diffuse wheezing despite treatment until day 9, when her breathing improved and she was no longer in hypoxemia. After an uneventful night, she was discharged on day 10 with improved cough and without SOB.

Case 2

A 31-year-old woman with allergic rhinitis and moderate persistent asthma called the office reporting SOB and wheezing for 4 days and was treated with increased inhaled corticosteroid and long-acting beta agonist combination (ICS-LABA) dose. She called again on day 6 of her symptom presentation for sudden-onset anosmia, postnasal drip, and constant wheezing and coughing despite use of albuterol every 4 hours. A test for COVID-19 infection was ordered, and her test result was positive. On day 8, she felt slight improvement in SOB and became ambulatory, but on the following day, she experienced abrupt increase in SOB and experienced sharp chest pain with a need to go to the ED. She was treated with bronchodilators and steroids. Her chest X-ray examination result was clear, and she was discharged from the ED; however, she continued to experience pronounced wheezing, SOB with minimal exertion, need for albuterol every 4 to 6 hours, and pain in her chest for 26 days.

Case 3

A 46-year-old woman on allergen immunotherapy for allergic rhinitis and asthma came for her scheduled visit. She reported to have experienced increased cough for 1 week. She was advised to increase the dose of ICS/LABA, continue antihistamines and montelukast, and call if she develops further symptoms. Five days later, she called the clinic with increased SOB, diarrhea, and severe weakness for 2 days. She received positive test results for COVID-19 infection on day 7. Despite increase in her ICS/LABA dose and oral steroids, she continued to have severe cough, SOB, chest pain, and no appetite. On day 10, she was admitted to the ED with acute renal failure, hypoxemia, and lymphopenia. On day 13, she started to improve and was discharged but continued to have increased need for albuterol and significant SOB with minimal exertion for 24 days.

Case 4

A 55-year-old man with asthma and history of recent fractured foot for which he received home health care called his home nurse reporting fever, diarrhea, and nausea for 3 days. His symptoms increased in the subsequent days with addition of severe SOB, wheezing, body aches, loss of appetite, and uncontrolled cough despite use of albuterol every 2 hours. He was on his way to the ED but was advised to stay home owing to the increase of patients infected with COVID-19, and a nurse was sent to his home for

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Table 1
Clinical Characteristics of Cases

	Case no. 1	Case no. 2	Case no. 3	Case no. 4
Age	34	31	46	55
Race	African American	African American	African American	African American
Sex	Female	Female	Female	Male
BMI	43.6	29.2	41.3	31.1
Age of asthma symptom onset	Childhood, Intubated as a child	Childhood	Childhood	Childhood
Age of asthma diagnosis (y)	21	Childhood	Childhood	30
Allergic comorbidities:				
Allergic rhinitis	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis
Chronic rhinosinusitis	–	–	–	–
Atopic dermatitis	–	–	–	–
Food allergy	–	Food allergy	Food allergy	–
Health comorbidities:				
Sleep apnea	Suspected (had PSG scheduled on the weekend of admission)	Negative	Negative	Positive
Allergic sensitivities	Tree, dust mite, dog, cockroach	Tree, grass, mold	Tree, grass, mold, dust mite	Tree, grass, mold, dust mite, cat
Controller baseline regimen:				
ICS/LABA (mcg)	200 Fluticasone furoate/50 vilanterol	Budesonide/formoterol	Budesonide/formoterol	200 Fluticasone furoate/50 vilanterol
LTRA	Montelukast	Montelukast	Montelukast	Montelukast
Biologic	Omalizumab	–	–	Omalizumab
Baseline prebronchodilator FEV1	99%	95%	89%	85%
PEFR baseline	400	370	410	350
PEFR on day of ED visit (L/min)	Not measured	230	290	260
Smoking status				
Tobacco	Former (15 pack history, quit 5 y ago)	Never smoked	Never smoked	Former (20 pack history, quit 7 y ago)
Oxygen saturation (at the peak of symptoms)	88%	100%	85%	94%
Presenting symptoms				
Fever (Tmax [°F])	Yes (104)	No	Yes (103)	Yes (102.7)
Cough	Yes	Yes	Yes	Yes
SOB	Yes	Yes	Yes	Yes
Wheezing	Yes	Yes	Yes	Yes
Arthralgia	Yes	Yes	Yes	Yes
Physical limitation	Yes	Yes	Yes	Yes
Anosmia	Yes	Yes	No	No
Diarrhea	Yes	No	Yes	Yes
Clinical course:				
Activity limitation	21 days	23 days	25 days	23 days
Level of care	ED + hospitalization	ED	ED + hospitalization	Frequent home nurse visits
Laboratory findings:				
WBC (4.0-10.0 K/mcL)	3.81 (low)		9.63	
Lymphocytes (1-4 K/mcL)	1.3		0.930 (low)	
AST (0-40 U/L)	42 (high)		51 (high)	
ALT (3-44 U/L)	49		25	
Creatinine (0.65-1.1 mg/dL)	1.16 (high)		1.14 (high)	
CRP (less than 0.5 mg/L)	6.1		69 (high)	
LDH (100-190 U/L)	196 (high)		389 (high)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; ED, emergency department; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LDH, lactate dehydrogenase; LTRA, leukotriene receptor antagonist; PSG, polysomnography; SOB, shortness of breath; WBC, white blood cell count.

treatment and evaluation. He was found to be in respiratory distress, which was treated with nebulized albuterol and home oxygen. A nasopharyngeal sample was taken which turned positive for COVID-19. He continued to experience fever, SOB, cough, body aches, and nausea, and remained bedridden for 3 weeks. He gradually improved after 20 days, but his cough and SOB remained to the point of needing nebulized albuterol every 4 to 6 hours for 27 days.

Discussion

We describe 4 patients with moderate to severe asthma who had a long COVID-19 infection course with minimum 24 days of respiratory symptoms. All cases needed ED visits, with 2 being admitted to the hospital. In all patients, the respiratory symptoms fluctuated. In 3 cases, the patients perceived improvement immediately before the peak of symptoms and their need for ED visits. All 4 patients reported symptoms of dyspnea, and general exhaustion occurred at an intensity not experienced during previous asthma exacerbations. They also noted that the duration of respiratory symptoms was much longer than that of previous asthma exacerbations. All 4 patients noted minimal improvement with recurrence within 2 hours of respiratory symptoms after albuterol use. This provides insight into potential manifestations of COVID-19 in patients with underlying asthma.

Members of the Coronaviridae family that are associated with self-limiting respiratory tract infections have been linked to asthma exacerbations.[4] The effect of more virulent species of coronavirus on asthma is not well known.

Initial studies from China did not find people with asthma at higher risk for severe respiratory syndrome because of COVID-19 infections.[2] Furthermore, they failed to adequately address asthma as a risk factor for severity of COVID-19 infection in their follow-up studies.[4] It is noteworthy that China has a much lower estimated prevalence of asthma than the United States, possibly because of underreporting, which can result in low power of these

studies to investigate asthma as a risk factor.[5] Thus, these early findings may not be applicable for patients with asthma in other countries. Indeed, recent reports from the Centers for Disease Control and Prevention indicate that chronic lung disease in 18- to 49-year-old age group is the second most prevalent underlying condition and that this was driven primarily by asthma.[6]

In our small case series, all patients were under the age of 55 years, African American, and on an ICS/LABA at baseline. Wheezing, which is not a symptom associated with COVID-19, was present in all patients. Moreover, 2 of 4 patients who had blood work had leukopenia. Furthermore, all 4 patients had a history of allergic rhinitis to tree pollen. Tree sensitivity is another variable that may have affected their asthma status and/or response to this virus and cannot be excluded as a cause for their exacerbation. Although a previous study found limited association between atopy and COVID-19 infection, this might not be applicable to our patient population and needs to be further investigated.[2] In addition, obesity was identified in 2 of these patients who required admission indicating a possible accumulative risk. Obesity is a known risk factor for poor outcome in asthma and appears to affect their outcome in the setting of COVID-19 infection.

The limitations of our study included a small sample size that was limited to a single site. This case series illustrates 4 cases of COVID-19 infection in patients with asthma. COVID-19 infection was associated with prolonged asthma exacerbation in these cases, especially in those with obesity who needed hospitalization. Our report calls for future multicenter studies on asthma during the COVID-19 pandemic.

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Rethinking respiratory function laboratories in the era of coronavirus disease 2019

Considerations for today and the day after

The members of the 2020 Proficiency Standards for Pulmonary Function Testing Committee of the American Thoracic Society recently raised concerns about pulmonary function testing (PFT) "as a potential avenue for COVID 19 [coronavirus disease 2019] transmission due to the congregation of patients with lung disease and because of the potential for coughing and droplet formation."[1] The committee recommended that "PFT be limited to tests that are only essential for immediate treatment decisions" and that "personal protective equipment (PPE) for healthcare workers should be discussed with local infection control teams."

These concerns are appropriate because spirometry (particularly when forced maneuvers are applied), exercise testing, methacholine challenge, and titration of continuous positive airway pressure for severe obstructive sleep apnea syndrome are all procedures able to generate aerosol. Moreover, although highly efficient antibacterial and antiviral filters are widely adopted as stated by the European Respiratory Society/American Thoracic Society guidelines,[2] ensuring body plethysmograph disinfection and air quality of the laboratory between patient visits is mandatory. However, how long can we postpone all these procedures? Common indications for PFT include evaluation of respiratory symptoms, such as cough and dyspnea; assessment and monitoring of disease severity and progression; monitoring for drug toxicity and efficacy; preoperative assessment[3]; evaluation of the effects of occupational or hazardous exposures; and participation in epidemiologic surveys. In particular, PFT is needed for the diagnosis and management of a considerable group of respiratory diseases, represents a major contributor to the *phenotypic* recognition of treatable traits of airway obstructive diseases (asthma and chronic obstructive pulmonary disease),[4] and is a key element of the future risk assessment of asthma.[5] Furthermore, the measurement of lung volumes is an essential part of severe asthma evaluation because the severity of asthma seems to be linked to enhanced air trapping rather than the level of airflow obstruction. Finally, PFT is used and recommended for the assessment and management of interstitial lung diseases, such as idiopathic pulmonary fibrosis; in particular, the pulmonary function indexes, such as forced vital capacity and carbon monoxide diffusion capacity, are part of the flowchart for pirfenidone or nintedanib prescription.[6]

We believe that in the COVID era, respiratory function laboratories should be considered places with a high intrinsic risk of respiratory infections and cross-contaminations. Until highly effective drug treatments or vaccines are available, we cannot assume that PFT can be performed without adequate PPE for health care personnel. Respiratory function laboratories should be considered highly specialized laboratory units directed by a chief with full responsibility for the safety of health care personnel and quality control. These laboratories should be located in dedicated areas with enough space and ventilation for patients undergoing respiratory function measurements. The use of air purification or ultraviolet and ozone decontamination systems should be applied according to the indications of the hospital or company management staff for rooms where aerosol-generating procedures are performed.[7,8] Time between each procedure should be enough to avoid aggregation and allow for disinfection of the exterior surfaces of the spirometer (and

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