A 16-Year-Old Boy With Cough and Fever in the Era of COVID-19

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A 16-year-old white boy with a history of chronic lung disease of prematurity, cough-variant asthma, and incidental lung nodules presented to the emergency center in spring 2020 with acute onset dry cough, shortness of breath, and fever. An initial history, gathered from his mother because of the patient's respiratory distress, revealed no recent travel. However, his mother is a health care worker at a hospital, and sick contacts included ongoing contact with a friend with cold-like symptoms. He had a variety of animals at home, including a dog, cats, fish, rodents, and reptiles. He had a history of vaping tobacco products >6 months ago. Fever and respiratory symptoms were associated with fatigue, chest tightness, abdominal pain, and myalgias. On examination, he was ill appearing and had tachycardia, tachypnea, borderline hypoxia with an oxygen saturation of 91% on room air, diminished breath sounds at the lung bases, and unremarkable abdominal examination results. A chest radiograph was consistent with the lung examination, revealing bilateral lower lobe hazy infiltrates. He showed initial improvement for 48 hours with antibiotics, intravenous fluid resuscitation, oxygen via nasal cannula, albuterol, and prednisone. Subsequently, he worsened with persistent high fever, increasing respiratory distress with pulmonary findings, and severe persistent epigastric pain, which added a layer of diagnostic complexity. As this patient's clinical course evolved and further history became available, pulmonary medicine and infectious diseases services were consulted to guide diagnostic evaluation and treatment of this patient early in the era of coronavirus disease 2019.

CASE HISTORY WITH SUBSPECIALTY INPUT

Dr Kelsey R. Anderson, Pediatric Resident, Moderator

A 16-year-old white boy with a history of chronic lung disease of prematurity, cough-variant asthma, and incidental lung nodules presented to the emergency center (EC) in spring 2020 with fever, cough, and shortness of breath for 3 days. The day before presentation, he sought severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing at a community clinic, and results remained pending.

On the day of presentation, he complained of daily fevers to 38.9°C, fatigue, coughing fits, chest tightness, abdominal pain, and myalgias. He denied sore throat, nausea, vomiting, diarrhea, adenopathy, or rashes. He reported improvement of respiratory complaints with albuterol. A history was obtained from his mother because of respiratory distress. He was fully immunized. He had not traveled. He had no known contact with persons with confirmed coronavirus disease 2019 (COVID-19), although a close friend had cold-like symptoms. He lived with his mother who was a health care

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Dr Anderson initiated this collaborative project, reviewed the literature, recruited and interviewed all subspecialists, and drafted and edited the manuscript; Dr Dean initiated this collaborative project, supervised the recruitment and interview of subspecialists, and critically revised the manuscript; Drs Villafranco, Hatzenbuehler Cameron, Schallert, Joshi-Patel, and Arrington contributed to the writing and revision of the manuscript; and all authors were involved in the patient's care and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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worker at a hospital and had no COVID-19 symptoms. They had animals at home, including a dog, 3 cats, a bearded dragon, fish, and 7 hamsters. He had a remote history of vaping tobacco products >6 months before admission.

In the EC, he was febrile to 38.5°C, pale, ill appearing, and in respiratory distress. His blood pressure was 140/80 mm Hg, his pulse was 132 beats per minute, his respiratory rate was 32 breaths per minute, and his oxygen saturation was 91% on room air. He had diminished breath sounds at the lung bases bilaterally but did not have wheezing or a prolonged expiratory phase. He was then placed on 2 L/minute of oxygen via nasal cannula, and oxygen saturations improved to 98%. His abdomen was soft, nondistended with normal bowel sounds, and diffusely tender without rebound. His laboratory tests revealed leukocytosis, with a leukocyte count of 15.2 $\times$ $10^3/\mu L$, a neutrophil predominance (absolute neutrophil count of 14.11 $10^3/\mu L$; 93%), and lymphopenia (absolute lymphocyte count of $740\times10^3/\mu L$; 4.9%). His C-reactive protein (CRP) level was elevated at 27 mg/dL (reference range: <1.0 mg/dL), although his procalcitonin, ferritin, liver enzyme, and lipase levels were normal. Rapid influenza and respiratory syncytial virus testing results were negative. An expanded polymerase chain reaction (PCR)–based respiratory panel for viral pathogens (including SARS-CoV-2) was sent. Blood cultures were obtained. A chest radiograph revealed bilateral hazy airspace opacities (Fig 1), which were not present 3 days before.

His heart rate and color improved with intravenous fluid resuscitation in the EC. He was started on ceftriaxone and azithromycin and admitted to the hospital on enhanced respiratory isolation precautions per infection control protocols.

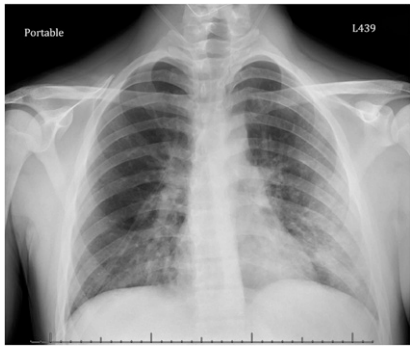

FIGURE 1
Chest radiograph with development of bilateral ground-glass airspace opacities, which are nonspecific. However, given history, this may represent pneumonia, and this pattern has been seen with COVID-19.

Dr Dean, will you explain the choice of antimicrobial agents in this patient? Were there any additional considerations for this patient with underlying asthma and suspected pneumonia?

Dr Andrea Dean, Pediatric Hospital Medicine

Although atypical or viral pneumonia was the most likely cause of community-acquired pneumonia (CAP) in this patient, because of concern for sepsis, empirical ceftriaxone was initiated to include coverage for *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. Azithromycin added *Mycoplasma pneumonia* coverage. The need for bronchodilators and steroids in patients with asthma and CAP should be guided by symptoms and examination results. Despite not showing objective signs of obstruction, our patient reported improved dyspnea with albuterol. Therefore, albuterol was scheduled for palliation of distressing symptoms. Steroids, however, were held because, at the time of presentation, evidence suggested worsened outcomes when steroids were used for COVID-19 pneumonia. Guidance has since changed.[1]

Dr Anderson

On hospital days 1 and 2, our patient showed mild overall improvement. Results of his initial and in-house SARS-CoV-2 tests were negative, and oral prednisone at 60 mg daily was started on day 1. A pulmonology consultation was placed given his underlying lung disease and new symptomatology.

Dr Villafranco, what was your initial impression about this patient? How concerned were you that his presentation was related to his known lung disease?

Dr Natalie Villafranco, Pediatric Pulmonary Medicine

This patient had a significant pulmonary history to consider, including chronic lung disease of prematurity, persistent asthma, and pulmonary nodules. In general, chronic lung disease of prematurity raises his risk for respiratory morbidity through childhood and adulthood,[2] including increased risk for wheezing and bronchodilator use,[3] more severe respiratory infections through childhood,[4] and obstruction defects on pulmonary function testing that may or may not respond to bronchodilator therapy.[5] He manifested all of these. In addition, he was being managed with serial imaging for lung nodules, which were incidentally found on an abdominal computed tomography (CT) scan, asymptomatic, <7 mm in size, and stable in size over a long period of time, suggesting that they were benign in origin[6–8] and not contributing to his acute clinical presentation.

Initially, his presentation was most concerning for atypical or viral pneumonia, including COVID-19, because community spread was active in the area at the time of admission. The treatment plan included a 5-day course of azithromycin and discontinuing steroids because of prevailing guidance to avoid them in patients

with COVID-19 and continued lack of wheezing.

Dr Anderson

Another in-house SARS-CoV-2 PCR test was sent, and prednisone was discontinued after the second dose. A confidential adolescent interview (home environment, education and employment, eating, activities, drugs, sexuality, suicide/depression, and safety [HEADSS] assessment) was taken. He endorsed vaping with tobacco products 3 weeks and tetrahydrocannabinol products 1 week before presentation.

Dr Dean, describe your approach to obtaining a HEADSS assessment in an admitted patient.

Dr Dean

Every adolescent patient needs a protected HEADSS assessment,[9] regardless of the reason for admission. When granted confidentiality, the teenager may disclose information that will guide the diagnostic or therapeutic plan. It is common for patients to not disclose high-risk behaviors initially,[10] and they should be offered multiple opportunities to do so. With each subsequent interview with the primary team and consultants, our patient not only became increasingly forthcoming about details of his vaping exposure but also later admitted to a 3-week history of chronic cough and intermittent fever before acute worsening of symptoms.

In the inpatient setting, obtaining a HEADSS assessment is not always possible on admission and can be delayed until appropriate (when the patient is stable or awake; often, it can be delayed by the primary team until after rapport is obtained). For this patient, it was only possible 30 hours into admission, when his respiratory distress and coughing fits had lessened and he could speak in complete sentences. In addition, because of COVID-19 infection control protocols that required caretakers to remain in the room at all times for persons under investigation, a private interview could not be performed until the COVID-19 testing result was negative.

Dr Anderson

Dr Villafranco, how did the information from the HEADSS assessment change your differential?

Dr Villafranco

The patient's recent vaping exposure, including tetrahydrocannabinol products, within a few weeks of presentation heightened our suspicion for electronic cigarette, or vaping, product use–associated lung injury (EVALI), although we continued to evaluate and treat for infectious causes. EVALI is a relatively new diagnosis, first identified in summer 2019, with Centers for Disease Control and Prevention surveillance beginning in August 2019 and documenting >2800 hospitalization cases and 68 known deaths as of February 2020.[11,12] It is an acute lung injury described as a constellation of signs and symptoms, including hypoxemic respiratory failure, dyspnea, constitutional symptoms (such as subjective fever and myalgias), and gastrointestinal symptoms (such as nausea and vomiting).[13,14] It can be difficult to distinguish from respiratory infection, and there is no diagnostic test available for EVALI, making it a diagnosis of exclusion.[15] It has been strongly associated with vitamin E acetate found in tetrahydrocannabinol vaping liquids.[16,17] The Centers for Disease Control and Prevention uses a 90-day window from exposure to symptoms for diagnostic criteria; however, most patients identified have symptoms within 1 week of vaping; other criteria suggest using a 30-day window.[15]

In addition to the time course of weeks between reported use and our patient's reported symptoms, his history of acute development of fever and cough was more consistent with acute infection than EVALI. He also seemed to be rapidly improving with antibiotics, a short course of steroids, and oxygen therapy, favoring an infectious process, including COVID-19, and the result of his second in-house SARS-CoV-2 PCR test remained pending.

Dr Anderson

After 48 hours of improvement, the patient worsened into day 3 of hospitalization. He had a persistent fever (maximum temperature of 38.8° C) and a frequent cough, and he continued to have abdominal pain, increasingly severe and localized to the epigastrium, without emesis or a change in bowel movements. During pain episodes, he had hypertension, tachycardia, and tachypnea difficult to differentiate from respiratory distress. Oxygen was increased to 4 L/minute after a desaturation to 86%. His lung and abdominal examination results remained unchanged. Lipase and liver enzyme levels, as well as the result of the stool occult blood test, were normal. A repeat complete blood cell count revealed resolved lymphopenia, and his CRP level remained elevated, although downtrending (21.4 mg/dL). Results of his initial expanded PCR-based respiratory viral panel (including parainfluenza, adenovirus, human metapneumovirus [hMPV], and rhinovirus) and the repeat SARS-CoV-2 PCR were negative. A repeat chest radiograph revealed increased bibasilar opacities without effusion or empyema. He requested more frequent albuterol for dry cough and morphine for abdominal pain, which had helped previously.

Dr Dean, how did you make sense of this patient's clinical status, especially his abdominal pain?

Dr Dean

Our patient's abdominal pain, which had been attributed to diaphragmatic

irritation from pneumonia, was worsening in the absence of obvious complications, such as a pleural effusion or empyema. Gastrointestinal pathologies were considered and ruled out. This enigmatic pain added a layer of diagnostic complexity to the case. In addition, despite his reported severe pain, providers were hesitant to use morphine, citing a lack of clear pain etiology, our patient's refusal of nonopioid analgesics, and his frustration at not receiving morphine as signs of drug seeking or possible opioid tolerance. A frank multidisciplinary discussion allowed us to address any internal biases that may have been impacting the care of our patient. Ultimately, his pain was incompletely understood, it was associated with vital signs changes and ongoing organic disease. Therefore, I opted to treat with therapeutic doses of morphine, to which our patient responded well. Lingering concerns of the team were allayed by an advanced plan to reconsider our approach if the pain did not improve simultaneously with other components of his disease.

Dr Anderson

Albuterol was again scheduled every 2 hours. Acetaminophen and ketorolac were scheduled, and morphine was ordered for breakthrough pain. Because of clinical worsening, radiographic findings, and an elevated CRP level, there was concern for antimicrobial failure, and vancomycin was added to his antibiotic regimen. Pediatric infectious diseases was consulted.

Dr Cameron, what was your initial impression? Specifically, were you concerned that this could be COVID-19?

Dr Lindsay Hatzenbuehler Cameron, Pediatric Infectious Diseases

Our additional history of subacute cough and low-grade fever leading up to presentation suggested a viral infection, followed by CAP. After 48 to 72 hours of antibiotic coverage for the most common CAP pathogens in his age group, therapy was expanded to cover for ceftriaxone-resistant *S pneumoniae* or methicillin-resistant *Staphylococcus aureus* infection. Viral respiratory pathogens circulating in the community at the time of his presentation included rhinovirus, adenovirus, hMPV, and SARS-CoV-2. However, SARS-CoV-2 prevalence was low; among children and adolescents tested at our institution, the cumulative number of cases was <10 from the time of widespread testing availability in early to mid-March 2020.

The result of his first SARS-CoV-2 test in the community was negative. SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) molecular testing was performed at our institution, and results were negative on two serial tests.

The performance of our institution's SARS-CoV-2 RT-PCR has a sensitivity of 98% and a specificity of 100%. This correlates with an analytical sensitivity to detect down to 40 copies of virus per test. The positive and negative predictive values are 100% and 96.9%, respectively. Because his SARS-CoV-2 RT-PCR test was obtained by personnel trained in performing a nasopharyngeal swab early in the course of his illness, we trusted his negative test result. The sensitivity of the test would have been increased only if a lower respiratory specimen were obtained. However, on the basis of his clinical course, he did not require intubation, and thus a lower respiratory specimen was not obtained.[18–21]

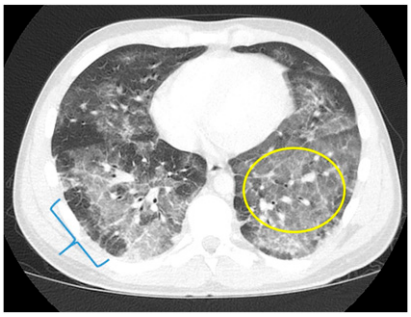

FIGURE 2
Axial CT image of the chest in a lung window reveals extensive GGOs with superimposed septal thickening creating a crazy paving pattern (circle) and with an area of subpleural sparing in the right lower lobe (bracket).

Dr Anderson

Despite broad-spectrum antibiotics, including methicillin-resistant *S aureus* coverage, on hospital days 4 and 5, our patient had worsened fever (maximum temperature of 39.4° C) and unremitting epigastric pain. His respiratory status was stable, and chest radiograph findings were improved. However, his CRP level had increased to 32 mg/dL. The result of a sputum culture was unrevealing.

A CT scan of the chest and abdomen was obtained. It revealed extensive diffuse airspace opacities, described as a "crazy paving" pattern (Fig 2). The one visualized nodule was stable from previous imaging. He had mild hepatosplenomegaly, but no clear explanation for abdominal pain.

Dr Schallert, will you explain these CT findings, including crazy paving?

Dr Erica K. Schallert, Pediatric Radiology

Crazy paving is a term to describe lung findings on the CT scan that consist of scattered or diffuse ground-glass opacities (GGOs) with superimposed linear thickening of the secondary lobule components.[22,23] The linear densities are the "grout" and outline the hazy irregular shapes, creatively "paver stones." GGO refers to increased hazy attenuation (white) but still allows visualization of the vascular network. This contrasts with consolidative opacity, in which the vasculature is obscured by the confluent whiteness. GGO on a microscopic level can either be filling of the alveoli with something other than air, including pus, fluid, blood, inflammation, or tumor cells, or it can be related to thickening of the interstitium or alveolar walls that is below the special resolution of the CT scan.[24]

As such, GGO has a wide differential. Crazy paving was initially thought to be specific for alveolar proteinosis, but the differential has widened to also include infection, pulmonary edema (including acute respiratory distress syndrome), organizing pneumonia, and, less likely in the pediatric age group, neoplasm.[22,23] COVID-19 would fall under the general infection category and EVALI under acute respiratory distress syndrome. Characteristic CT imaging findings for COVID-19 in the pediatric population are bilateral peripheral predominant GGOs and/or consolidation in the mid and lower lung zones.[25,26] Characteristic CT imaging findings of EVALI in the pediatric population are bilateral symmetric GGOs with subpleural sparing, consolidation, and lower lobe predominance.[27,28] Crazy paving has been described in both.[25–28] In our patient, the few areas of subpleural sparing point more toward EVALI.

Dr Anderson

Dr Cameron, what were your thoughts on the infectious differential provided by radiology?

Dr Hatzenbuehler Cameron

The interstitial pattern of disease on his CT scan raised the concern of viral pneumonitis (adenovirus, influenza, hMPV, parainfluenzae, SARS-CoV-2, cytomegalovirus [CMV], or Ebstein-Barr virus [EBV]), antimicrobial failure, endemic fungal pneumonia, *Legionella pneumophila*, *Pneumocystis jirovecii* pneumonia, or a noninfectious etiology. CMV, EBV, and *P jirovecii* pneumonia were thought to be unlikely in an immunocompetent, HIV-negative host. Despite his animal exposures at home, zoonoses were considered unlikely. His pulmonary nodules were previously evaluated, with a negative result for the fungal antibody panel and a negative QuantiFERON-TB Gold Plus result. The nodules also were unchanged, which supported against a chronic infectious etiology or that the nodules were clinically pertinent to his acute illness. A diagnostic bronchoscopy was considered.

Dr Anderson

Dr Villafranco, what were your considerations when approached by the primary and infectious disease teams about bronchoscopy?

Dr Villafranco

The primary indication for flexible bronchoscopy in this patient is diagnostic: to obtain bronchoalveolar lavage samples for further infectious disease testing and cytology.[29,30] Because we had serological, PCR, and sputum culture data for the most likely infections, bronchoscopy samples for infection would be of low yield. Cytology helps to identify any signs of pulmonary hemorrhage and cellularity, but this is not specific for any diagnosis. There is no indication for bronchoscopy in patients to identify EVALI because there is no diagnostic test or pathognomonic finding.[31]

Bronchoscopy is considered a high-risk aerosol-generating procedure[32,33] and in the COVID-19 environment, is generally limited to emergent or urgent indications to prevent unnecessary exposure of health care workers as well as to spare personal protective equipment (PPE).[34] Given that our patient's symptomatology was overtly concerning for COVID-19, our section recommended full PPE, including an N95 mask and face shield, if bronchoscopy was performed. However, the overall benefit of this procedure was still not clear with the risk of anesthesia, potential exposure of health care workers, and PPE shortages, and it was not classified as emergent or urgent.

Dr Anderson

On day 6 of hospitalization, infection control approved repeat COVID-19 testing specifically aimed to alleviate ongoing anxiety of the staff preparing to perform bronchoscopy despite agreeing with the infectious disease team that previous negative results were reliable. When that test result returned negative later that day, prednisone at 60 mg daily for treatment of EVALI was initiated.

Dr Villafranco, what about the patient's clinical course had moved EVALI up on your differential as well as influenced the decision to treat with steroids?

Dr Villafranco

At this point, our patient's negative results on the extensive infectious disease workup, increasing transparency about recent and repeated vaping exposure of tetrahydrocannabinol products, and imaging findings pointed to an EVALI diagnosis. We started a two-week course of steroids in addition to continued supportive care. Evidence for treatment of EVALI with steroids is based on case reports and is not well studied, but multiple reports have revealed rapid improvement with variable dosing and time course.[11,14,35] We agreed as a team that bronchoscopy would be reconsidered only if he clinically worsened or did not improve after steroid initiation.

Dr Anderson

On day 7 of hospitalization, 24 hours after starting steroids, our patient's fever resolved and did not recur for the remainder of the hospitalization. He tolerated weaning of oxygen, and his abdominal pain also began to improve, albeit more slowly. His blood pressure elevation became unrelated to pain, and nephrology diagnosed steroid-induced hypertension.

He was tolerating room air by hospital day 10 and was discharged on day 14. He completed a 10-day course of antibiotics with amoxicillin and clavulanic acid and doxycycline, and he was discharged with a two-week prednisone wean as well as scheduled ibuprofen and acetaminophen with limited supply of

hydrocodone-acetaminophen for breakthrough pain.

Dr Dean, what were the discharge criteria for this patient? How has COVID-19 changed your usual discharge process?

Dr Dean

Pain control proved the final barrier to discharge and was addressed cautiously, with special attention to shared decision-making with the family, given the early concerns about pain management explained previously. In addition, discharge criteria in the era of COVID-19 must be considered carefully for all patients because early outpatient follow-up was not readily available at the time, and return trips to the EC carry exposure risk. Therefore, our patient was slowly transitioned to intermittent dosing of oral opioids, and he was monitored for tolerance of the regimen longer than he might have been otherwise.

Dr Anderson

All remaining studies revealed no infectious etiology of disease, including the following: atypical pneumonia panel, fungal complement fixation, sputum fungal and mycobacterial cultures, CMV immunoglobulin M and immunoglobulin G, EBV antibody panel, and multiple blood cultures. Given clinical improvement, bronchoscopy was not pursued. Workup for autoimmune disease associated with pulmonary hemorrhage was also unremarkable, including the antinuclear antibody profile and myeloperoxidase and neutrophil protein proteinase-3 antineutrophil cytoplasmic antibodies, C3, and C4 levels.

Our patient had a telemedicine appointment with his pulmonologist 8 days after discharge and reported resolution of cough, chest tightness, and abdominal pain. His repeat laboratory test results had normalized, including the CRP level. A chest radiograph revealed resolution of bilateral airspace opacities.

FINAL THOUGHTS AND DISCUSSION: DR ANDERSON

Initially, there was high suspicion for COVID-19 given the timing of our patient's presentation and his constellation of signs and symptoms. However, SARS-CoV-2 testing results were negative, so alternative diagnoses were pursued, including CAP and staphylococcal pneumonia. When treatment failed, our patient's family and medical team remained worried for a missed SARS-CoV-2 diagnosis, which drove repeated testing, even when further vaping history was disclosed and multiple negative results made a diagnosis of EVALI increasingly likely. Availability bias likely contributed because despite low prevalence at the time, there was media saturation and constant institutional reminders of COVID-19, especially for frontline providers whose practice was rapidly changing because of the emergence of this disease. Indeed, COVID-19 considerations affected nearly every step in our patient's care, from infection control protocols delaying a confidential interview to PPE shortages being considered for bronchoscopy. More importantly, because EVALI is only considered in the absence of an alternative likely diagnosis, the presence of COVID-19 complicated the ability to arrive at his ultimate diagnosis or treat on the basis of a presumptive diagnosis given guidance at the time to avoid steroids in COVID-19.[1,12] Ultimately, a crazy paving pattern on the CT scan, followed by a fourth and final negative SARS-CoV-2 PCR test result, led to his diagnosis of EVALI and initiation of treatment.

COVID-19 and EVALI are both newly described diseases with significant overlap in their clinical features, namely constitutional and respiratory symptoms. Gastrointestinal symptoms, including abdominal pain, are also common in both EVALI (77%)[13,14] and COVID-19 (up to 40%).[36] As in our patient's case, these symptoms can be severe and predominate in either disease.[36–39] In addition, radiologic findings are similar.[25–28] For our patient, the EVALI diagnosis is favored by multiple negative SARS-CoV-2 PCR test results and that none of his close contacts, including his mother, developed symptoms of COVID-19. Finally, our patient's robust response to steroids and, in retrospect, the worsening of his disease while steroids were suspended would be unlikely in COVID-19 but has been described in some EVALI cases.[11,14,35] As the number of cases of these diseases increases, reporting and research will lead to more nuanced descriptions that can guide care.

ABBREVIATIONS

CAP: community-acquired pneumonia
CMV: cytomegalovirus
COVID-19: coronavirus disease 2019
CRP: C-reactive protein
CT: computed tomography
EBV: Ebstein-Barr virus
EC: emergency center
EVALI: electronic cigarette, or vaping, product use–associated lung injury
GGO: ground-glass opacity
HEADSS: home environment, education and employment, eating, activities, drugs, sexuality, suicide and depression, and safety
hMPV: human metapneumovirus
PCR: polymerase chain reaction
PPE: personal protective equipment
RT-PCR: real-time polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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