Case Report

A Case Series of Patients Coinfected With Influenza and COVID-19

Venu Madhav Konala, MD, FACP, CACP1, Sreedhar Adapa, MD, FACP, FASN2, Srikanth Naramala, MD, FACP, CCD2, Avantika Chenna, MD, FASN3,4, Shristi Lamichhane, MBBS5, Pavani Reddy Garlapati, MD5, Mamtha Balla, MD, MPH6,7, and Vijay Gayam, MD5

Abstract
Coronavirus disease 2019, also called COVID-19, is a global pandemic resulting in significant morbidity and mortality worldwide. In the United States, influenza infection occurs mainly during winter and several factors influence the burden of the disease, including circulating virus characteristics, vaccine effectiveness that season, and the duration of the season. We present a case series of 3 patients with coinfection of COVID-19 and influenza, with 2 of them treated successfully and discharged home. We reviewed the literature of patients coinfected with both viruses and discussed the characteristics, as well as treatment options.

Keywords
coronavirus disease 2019, COVID-19, influenza A, influenza B, acute respiratory distress syndrome

Introduction
Coronavirus disease 2019, also called COVID-19, is a global pandemic resulting in significant morbidity and mortality. The cluster outbreak of cases of pneumonia from severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) was reported in December 2019 in Wuhan, China.1 The COVID-19 has spread across the world at a fierce pace, and the United States has the highest number of infected patients, which led to the highest mortality in the world.2

The influenza pandemic occurs in the winter, and the mode of transmission is the same as that of COVID-19. The most common clinical symptoms in influenza are fever, cough, shortness of breath, fatigue, headache, and myalgia, which are similar to COVID-19.3 There have been only a few cases of coinfection from influenza and COVID-19 reported before. In this article, we describe 3 cases of coinfected cases of influenza and COVID-19 in the United States.

Case Series

Patient 1
A 57-year-old male presented to the emergency department with a complaint of on and off fever as well as dry cough going on for 2 weeks and worsening shortness of breath for 2 days. He initially had a dry cough, which later became productive with brownish sputum. The fever was associated with headaches, sore throat, and myalgia and did not subside with ibuprofen and paracetamol. He denied any recent sick contact or recent travel. The patient’s past medical history was significant for hypertension, diabetes mellitus, and myocardial infarction–automatic implantable cardioverter defibrillator (AICD) insertion. The patient denied any history of smoking, alcohol use, or illicit drug use.

On admission, the patient had a temperature of 101.3 °F, pulse rate of 123 beats per minute, respiratory rate of 22 breaths per minute, blood pressure of 100/90 mm Hg, and...
Oxygen saturation of 92% on room air. Physical examination was significant for right basal crackles and palpable AICD.

The electrocardiogram showed sinus tachycardia without ST-T wave changes and normal QTc interval. Chest X-ray showed septal bilateral patchy lung infiltrates versus atelectasis (Figure 1). The patient underwent computed tomography (CT) of the chest without contrast, which showed patchy bilateral ground-glass opacities in the periphery of both lungs (Figure 2) with suspicion for COVID-19 given clinical symptoms and radiological findings.

The patient was admitted to the medical floor for treatment of pneumonia as well as to rule out COVID-19 infection. Influenza and COVID-19 nasopharyngeal swabs were sent. The patient was started on 3 L of oxygen via nasal cannula with oxygen saturations above 95%. He was started on antibiotics with ceftriaxone and azithromycin. The patient was positive for both COVID-19 and influenza A. The patient was then started on oseltamivir along with hydroxychloroquine with QTc monitoring after an infectious disease and pulmonary consult. The patient completed a 5-day course of ceftriaxone, azithromycin, hydroxychloroquine, and oseltamivir. The patient remained afebrile and was saturating above 95% on room air for 72 hours and was discharged home.

**Patient 2**

A 35-year-old female presented with fever, headaches, dry cough, worsening shortness of breath, and diarrhea for 5 days. The highest recorded fever at home was 104 °F, which responded to acetaminophen. The patient worked as an airline manager and has not traveled, but has come in contact with a large number of international travelers. Her past medical history was significant for sickle cell trait.

On admission, the patient’s temperature was 103.3 °F, pulse rate of 121 beats per minute, respiratory rate of 18 breaths per minute, blood pressure of 117/70 mm Hg, and oxygen saturation of 97% on room air. Physical examination was significant for tachycardia, respiratory distress, and fine crackles on the left lower chest on auscultation.

The electrocardiogram showed sinus tachycardia at a ventricular rate of 121 beats per minute without ST-T wave changes along with normal QTc intervals. A portable chest X-ray reported moderate bilateral alveolar infiltrates right more than left (Figure 3). CT scan of the chest without contrast revealed extensive scattered bilateral infiltrates right greater than left (Figure 4). Given the patient’s history as well as radiological findings, COVID-19 was suspected.

The patient subsequently tested positive for influenza A and COVID-19. Blood and urine cultures revealed no
growth. The patient was treated with intravenous (IV) ceftriaxone, IV azithromycin, and oseltamivir. She also received hydroxychloroquine after COVID-19 was positive. Corrected QTc interval was monitored regularly. After consecutive 6 days of fever, the patient remained afebrile from day 7 onward. Oxygen saturation was maintained with oxygen 2 to 3L via nasal cannula. The patient was discharged home after she reported symptomatic improvement in shortness of breath and fever.

**Patient 3**

A 68-year-old female presented to the emergency department with a chief complaint of altered mental status and worsening shortness of breath along with mild diarrhea. Detailed history could not be elicited because of altered mental status. Her past medical history was significant for diabetes mellitus, hypertension, and gastroesophageal reflux disease. On arrival to the emergency department, the patient was saturating 62% on room air, which improved to 90% with oxygen via a nonrebreather mask. The patient was tachycardic and tachypneic on the presentation at 119 beats per minute and respiratory rate at 28 breaths per minute, respectively. Her temperature was 102 °F, blood pressure of 100/82 mm Hg. Physical examination was significant for a confused patient in acute distress with tachypnea and tachycardia along with bibasal crackles. The patient’s condition continued to deteriorate and required intubation and ventilation due to respiratory muscle fatigue.

A portable chest X-ray revealed mild-to-moderate pulmonary venous congestion, hazy airspace opacities bilaterally, which may represent diffuse pneumonia versus alveolar edema and very small bilateral pleural effusions (Figure 5). CT of chest without contrast showed extensive scattered bilateral infiltrates (Figure 6). Electrocardiogram revealed a ventricular rate of 112 beats per minute with a corrected QTc interval of 450 ms.

The patient tested positive for COVID-19 and influenza A and was treated with ceftriaxone, azithromycin, hydroxychloroquine. The patient also had acute kidney injury with a history of chronic kidney disease and improved with IV hydration. The patient, unfortunately, had a cardiac arrest on day 1 of admission with unsuccessful cardiac resuscitation.

The laboratory testing for all patients are summarized in Table 1. All patients had lymphopenia along with elevated C-reactive protein, erythrocyte sedimentation rate, creatinine kinase, fibrinogen, D-dimer, interleukin-6 levels, lactic acid, and lactate dehydrogenase.

**Discussion**

The novel coronavirus spike (S) protein attaches to the membrane-bound angiotensin-converting enzyme 2 (ACE 2) and cleaved by serine proteases to gain access into the human
ACE 2 is widely distributed in the lungs, kidneys, gastrointestinal tract, oral, and nasal mucosa. COVID-19 causes activated T-cell response and increased pro-inflammatory cytokines levels. In severe cases, these increased levels can cause a cytokine storm and damages healthy tissue than the virus.4,5

COVID-19 causes mostly fever, cough, sore throat, and shortness of breath, which in most cases are self-limiting. Some individuals harbor the virus and are asymptomatic. They play a crucial role in the spread of the virus in the community.1

COVID-19 primarily affects the lungs causing dyspnea, hypoxia, and can cause severe infections resulting in acute respiratory distress syndrome (ARDS). In severe cases, patients often need intensive care unit admission causing multi-organ failure and death.1

COVID-19 co-circulates in the environment along with other respiratory viruses and, most importantly, influenza. The study from a hospital in Wuhan, which analyzed the epidemiological, demographic, and laboratory data from the COVID-19 and influenza cases visited between January 2017 and February 2020. There was a decreased number of influenza A and B cases in 2020 compared with the previous years. COVID-19 interfered with the seasonal influenza epidemic. There were 9 co-infection cases of influenza and COVID-19 reported in 1054 cases.6 As per Centers for Disease Control and Prevention estimates from 2018-2019, approximately 35 million people were infected with influenza that resulted in approximately half million hospitalizations. Thirty-four thousand patients died from influenza last year.3

A double-center study was done in China to analyze coinfections of common respiratory pathogens in COVID-19. A total of 68 patients with SARS-CoV-2 infection were recruited, 38 from Wuhan and 30 from Qingdao. Among them, 24 (80%) patients from Qingdao had an immunoglobulin M antibody against 1 respiratory pathogen, compared with only 1 patient in Wuhan. The most common respiratory pathogens detected were influenza A, influenza B in the majority of cases, followed by *Mycoplasma pneumoniae* and *Legionella pneumophila*. This shows that the coinfection pattern differs significantly depending on the geographic area.7

In an experience described by Wuhan, only 5 patients among 115 were coinfected with influenza and COVID-19. In those 5 patients, 3 patients had influenza A, and 2 patients had...
| Drug used                                                                 | Phase/number of study participants | Type of study                                      | Mode of administration |
|--------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------|------------------------|
| Standard treatment with or without lopinavir plus ritonavir, with or without arbidol | Phase 4/125 | Open-labelled, randomized controlled clinical trial | Oral                   |
| Hydroxychloroquine sulfate vs placebo                                   | Phase 4/202 | Two-arm, open-label, pragmatic randomized controlled trial | Oral                   |
| Colchicine or placebo                                                    | Phase 3/6000 | Randomized, double-blind, placebo-controlled multicenter study | Oral                   |
| Convalescent plasma                                                     | Phase 2/20 | Open-label, phase 2A single center clinical trial | IV                     |
| Lopinavir/ritonavir, ribavirin and interferon-β-1b combination vs lopinavir/ritonavir alone | Phase 2/70 | Prospective open-label randomized controlled trial | Lopinavir/ritonavir, ribavirin—oral, interferon-β-1b—subcutaneous |
| Recombinant human interferon-α-1b (low-risk group)                      | Phase 3/2944 | Open-label, nonrandomized, parallel assignment | Recombinant human interferon-α-1b—nasal |
| Recombinant human interferon-α-1b and thymosin-α-1 (high-risk group)   | Phase 3/1944 | Open-label, nonrandomized, parallel assignment | Thymosin-α-1—subcutaneous |
| Mesenchymal stem cell in treating pneumonia patient’s vs placebo with standard treatment in both arms | Phase 1/20 | Open-label, nonrandomized, parallel assignment | IV                     |
| Natural killer cells treatment in pneumonia patient’s vs placebo with standard treatment in both arms | Phase 1/30 | Open-label, nonrandomized, parallel assignment | IV                     |
| Anti-SARS-CoV-2-inactivated convalescent plasma                          | NA       | Prospective observational case only                | IV                     |
| Favipiravir combined with chloroquine phosphate vs favipiravir vs placebo | Phase 2/3—150 | Multicentered, 3-armed, randomized, double-blinded, controlled study | Both drugs—oral |
| Nitric oxide gas inhalation therapy for mechanically ventilated patients with severe acute respiratory syndrome vs placebo | Phase 2/200 | Multicenter randomized controlled trial with 1:1 individual allocation | Inhalation |
| Low-dose chloroquine vs high-dose chloroquine                            | Phase 2b/200 | Phase IIb, double-blind, randomized adaptive clinical trial | Oral                   |
| Sargramostim vs placebo along with standard of care in both arms        | Phase 4/80 | Prospective, randomized, open-label, interventional study | Inhalation or IV |
| Remdesivir 5 days vs 10 days along with SOC                             | Phase 3/400 | Open-label, randomized, parallel assignment       | IV                     |
| Remdesivir 5 days vs 10 days along with SOC                             | Phase 3/600 | Open-label, randomized, parallel assignment       | IV                     |
| Vitamin C                                                                | Phase 2/140 | Open-label, randomized, parallel assignment       | IV                     |
| DAS181                                                                   | Phase 3/250 | Randomized placebo-controlled study, parallel assignment | Nebulizer, inhalation |
| Sarilumab                                                                | Phase 2-3/250 | Randomized, double-blind, placebo-controlled, parallel assignment | IV                     |
| Pirfenidone                                                              | Phase 3/294 | Open-label, randomized, parallel assignment       | Oral                   |
| Sarilumab                                                                | Phase 2-3/300 | Randomized, double-blind, placebo-controlled, parallel assignment | IV                     |

(continued)
influenza B. All the patients had a fever, cough, and shortness of breath. Two patients developed fatigue, myalgia, headache, and expectoration. Three patients had pharyngalgia, which appeared more in the patients who developed coinfection. Only 1 patient developed chest pain and hemoptysis. The laboratory data revealed lymphocytopenia and elevated C-reactive protein in 4 patients, elevated transaminases, and procalcitonin levels in 2 patients. Lymphocyte count improved during the remission of the disease. The renal function and coagulation function was normal in these patients. Only 1 patient among the 5 patients developed ARDS and needed noninvasive-assisted ventilation and improved. The chest CT of the patient who developed ARDS had significant ground-glass opacities and subsegmental areas of consolidation that correlated with the clinical picture. The renal function and coagulation function was normal in these patients. Only 1 patient among the 5 patients developed ARDS and needed noninvasive-assisted ventilation and improved. The chest CT of the patient who developed ARDS had significant ground-glass opacities and subsegmental areas of consolidation that correlated with the clinical picture.

Wu et al reported a case of a 69-year-old male who presented with fever and dry cough after visiting Wuhan during the time of the COVID-19 outbreak. The patient’s CT revealed ground-glass consolidation in the right lung inferior lobes. COVID-19 was suspected, nasopharyngeal swab specimen resulted negative for SARS-CoV-2 on repeated testing, but yielded positive for influenza A. The patient was discharged on oral oseltamivir and was instructed to remain in isolation at home. Subsequently, in a week, the patient developed ARDS and lymphopenia. Repeated testing by nasopharyngeal swab and sputum sample was negative. The patient was subsequently intubated, and finally, bronchoalveolar lavage fluid was tested positive for SARS-CoV-2. This case highlights that both influenza and SARS-CoV-2 mimic the clinical picture, and often the diagnosis of COVID-19 can be missed with false-negative tests for the upper respiratory specimen. If the suspicion for COVID-19 is high, repeated testing should be performed.

Four cases of coinfection with SARS-CoV-2 and influenza were reported from Iran. Three of the patients were males, relatively younger, except for 1 patient, and only 1 patient has comorbidities. All the patients had a cough, dyspnea, and fever, while the majority had headache and myalgia. One patient had gastrointestinal symptoms. The majority had lymphopenia and elevated inflammatory markers. All the patients had radiological abnormalities. Significant renal failure was noted in 1 patient, and liver failure was noted in 2 patients. No outcomes were described in the patients.

Drug used | Phase/number of study participants | Type of study | Mode of administration
---|---|---|---
Remdesivir vs lopinavir/ritonavir vs interferon-β-1A vs hydroxychloroquine vs SOC | Phase 3/3100 | Randomized, multicenter, adaptive parallel assignment | Remdesivir—IV, lopinavir/ritonavir—oral, interferon-β-1A—subcutaneous, hydroxychloroquine—oral
Esocin vs SOC | Phase 2-3/120 | Double-masked, nonrandomized, parallel assignment | Oral
Bevacizumab | Phase 2/20 | Open-label, single group assignment | IV
Fingolimod | Phase 2/30 | Open-label, nonrandomized, parallel assignment | Oral
Favipiravir combined with tocilizumab vs favipiravir vs tocilizumab | 150 | Open-label, multicenter, randomized, parallel assignment | Favipiravir—oral, Tocilizumab—IV
Hydroxychloroquine + azithromycin vs hydroxychloroquine | Phase 3/440 | Open-label, randomized, parallel assignment | Oral
Darunavir and cobicistat | Phase 3/30 | Open-label, randomized, parallel assignment | Oral
BCG vaccine | Phase 3/4170 | Two group, multicenter, open-label randomized parallel assignment | Intradermal
Combination of lopinavir/ritonavir and interferon-β-1b | Phase 2-3/194 | Recursive 2-stage group sequential multicenter placebo-controlled double-blind randomized parallel assignment | Lopinavir/ritonavir—oral, interferon-β-1b—subcutaneous

Abbreviations: IV, intravenous; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2; NA, not applicable; SOC, standard of care; BCG, Bacillus Calmette-Guérin.
There is no proven therapy for COVID-19 till now; meticulous supportive care holds key. The patients are getting treated with hydroxychloroquine, azithromycin, as seen in our case series and in severe cases, interleukin-6 antibodies. Novel nucleoside analog-like remdesivir was also used. The treatment with steroids is controversial. There have been many emerging and experimental therapies described. Many clinical trials are underway across the globe to check the efficacy of different medications in COVID-19. In a few centers, the convalescent serum has been used. Patients with influenza should be treated with oseltamivir. Multiple clinical trials are under investigation as summarized in Table 2.11

Influenza and SARS-CoV-2 cause mostly similar symptoms, and the coinfection did not significantly worsen the symptoms or outcomes.

**Conclusion**

Influenza and SARS-CoV-2 coinfection can occur in patients with similar symptoms. The coinfection did not significantly worsen the symptoms and outcomes. It is essential to recognize coinfections as the treatment can be completely different. Patients should get vaccinations for common respiratory pathogens if available, to reduce the risk of coinfection.

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**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article. For patient 3, consent was obtained from next of kin.

**ORCID iDs**

Venu Madhav Konala https://orcid.org/0000-0003-1953-8815
Sreedhar Adapa https://orcid.org/0000-0001-5608-5654
Srikanth Naramala https://orcid.org/0000-0003-1238-856X
Shristi Lamichhane https://orcid.org/0000-0001-9427-0340
Vijay Gayam https://orcid.org/0000-0001-5194-9134

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