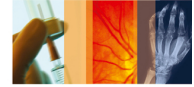


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The Early Natural History of SARS-CoV-2 Infection: Clinical Observations From an Urban, Ambulatory COVID-19 Clinic

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In March, 2020, weeks before the coronavirus disease 2019 (COVID-19) pandemic surge was predicted to arrive in Massachusetts, two of us (JJ, LH) designed an ambulatory clinic specifically to care for patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). None of the hundreds of research reports published to date addressed caring for patients infected with SARS-CoV-2 in the ambulatory setting, and it became clear that one of the first challenges we faced was to gain an understanding of the typical presentation and early natural history of mild and moderate COVID-19 to guide our care during the pandemic.

While we had access to state laboratory real-time reverse transcription polymerase chain reaction diagnostic testing for SARS-CoV-2, the delay of four to five days made the results impractical for clinical management. Routine laboratory studies, likewise, did not appear to be clinically useful. We focused, instead, on trying to discern patterns from a detailed history and limited physical exam that might distinguish COVID-19 from other similar illnesses.

Initially some cases of COVID-19 appeared to be identical to influenza, upper respiratory tract, lower respiratory tract infections, gastroenteritis and community acquired pneumonia. After caring for more than a thousand patients in our COVID clinic, however, we came to suspect that many moderate and severe cases of COVID can be diagnosed by a careful history.

At the outset, patients with SARS-CoV-2 infection may be asymptomatic or experience symptoms indistinguishable from a variety of acute viral and bacterial infections. In a retrospective study of 191 patients admitted to two hospitals in Wuhan, China, the initial several days of SARS-CoV-2 infection involved fever (94%) and cough (79%).¹ But these presentations were likely biased by being only those of hospitalized patients, and hospital admission was often predicated on testing positive for COVID-19 in an ambulatory “fever clinic”. Referral to a fever clinic in Wuhan, China required the presence of both fever and at least one respiratory symptom, likely limiting the spectrum of disease

described in these and other early studies, for example, by excluding patients with predominantly gastrointestinal symptoms.^{2,3}

In our clinic, patients with various permutations of mild symptoms including nasal congestion, cough without fever, sore throat, diarrhea, abdominal pain, headache, myalgias, back pain and fatigue have tested positive for COVID-19. We have also cared for many patients who experienced severe symptoms during the initial days including fever, cough, myalgias and exhaustion. These initial days of infection can range from mild upper respiratory symptoms, cough and fatigue suggestive of bronchitis, sore throat and fever, abdominal pain with diarrhea or influenza-like illnesses. Of note, though fever is a common symptom over the course of COVID-19, temperature elevations can be mild, particularly at the outset of illness.⁴ One of the only early hints to the diagnosis is loss of smell⁵ which many of our patients report losing during the first few days of illness.

Though many patients will recover from their initial symptoms over the course of two to three weeks, for a sizable proportion of patients, their clinical course worsens, with dyspnea setting in typically between the fourth and eighth day of illness, although we have also seen some patients in whom dyspnea first develops more than 10 days after the onset of symptoms. The onset of dyspnea is the point at which COVID-19 can begin to be discerned from other common illnesses.

Some patients who develop dyspnea progress to critical illness, while others have a stable, persistent course that spontaneously resolves after several days or weeks and, in our clinical experience, can often be safely managed at home. We have found these first days after the onset of dyspnea to be critical for monitoring patients frequently by televisits or in-person evaluations. The most useful factor to monitor is oxygen saturation which often drops precipitously with exertion, even in some previously healthy patients. Similar to published observations, several clinical factors appear to predict clinical worsening in our experience, including: older age, diabetes, cardiovascular disease, obesity and

hypertension.⁶ Having immigrated from Central America and living in close quarters with multiple family members or different families have been particularly important risk factor for disease progression in our patients.

Distinguishing COVID-19 from other serious, treatable conditions is essential. Community acquired pneumonia, especially with atypical organisms such as *Legionella*, may present quite similarly to COVID-19.⁷ There may be some clues, however, that can assist clinicians in distinguishing the two diagnoses. The classic progression of *Legionella* pneumonia initially begins with fever and fatigue, followed by cough shortly thereafter – dyspnea would only be expected in cases in which the pneumonia progressed to become more severe. In contrast, in patients with COVID-19 we often see the appearance of cough and fever at the onset with dyspnea occurring a few days later, sometimes even after the fever has abated.

Clinically, COVID-19 respiratory symptoms appear to be most similar to those caused by *Pneumocystis jirovecii* pneumonia, a pulmonary infection predominantly affecting the alveoli. We have found that, similar to *Pneumocystis* pneumonia, a precipitous drop in oxygen saturation with exertion is highly suggestive of SARS-CoV-2 infection. In the case of *Pneumocystis* pneumonia, however, the dyspnea typically develop insidiously over weeks, not days.

Post-viral pneumonia also has many similarities to COVID-19, but might be distinguishable in some cases by a careful history. Cough and fatigue may be the initial presentation in both, but the next stage is different. While increasing fever and productive cough might be symptoms of post-viral pneumonia, in COVID-19 we typically note worsening dyspnea without productive cough.

Similarly, during the initial days of infection, both influenza and COVID-19 may have identical presentations, but thereafter the progression of the two infections diverges. In uncomplicated influenza, it would be unusual to develop the onset of dyspnea 4 to 8 days after symptoms began.

While patients with influenza may develop mild dyspnea, we would expect the dyspnea to improve gradually over the following days or weeks with an uncomplicated influenza infection. In addition, patients with rare viral pneumonia from influenza tend to deteriorate rapidly within the first 2 to 3 days of infection, unlike patients with COVID-19 who do not tend to deteriorate until later in their course of illness.

COVID-19 can also present similarly to Streptococcal pharyngitis, viral sinusitis, acute pericarditis and other common infections, but in each case, the key distinction is the development of dyspnea several days after the onset of infection, even as the other symptoms may be improving.

Given the extensive media attention regarding the serious consequences of COVID-19, there is an understandably high level of anxiety in the community. One common cause of shortness of breath in our clinic has been anxiety combined with viral-type symptoms. Key aspects of anxiety-induced shortness of breath that have helped us distinguish anxiety-induced dyspnea from SARS-CoV-2-induced dyspnea is the onset: with anxiety, onset is often immediately after the first symptoms of infection while with SARS-CoV-2 dyspnea occurs several days after the initial symptoms begin. The description of dyspnea is often helpful as well. In our patients with COVID-related anxiety, the dyspnea tends to occur at rest or when trying to fall asleep but does not become more pronounced when participating in daily activities. Patients with COVID-related anxiety often describe the sensation of not being able to get enough air into their lungs, while with SARS-CoV-2 infection dyspnea is consistently worse with exertion. While dizziness might occur in both conditions, it too is more likely to be present at rest with anxiety and with exertion in COVID-19 disease. When a pulse oximeter is available, a normal oxygen saturation with ambulation helps confirm one's clinical suspicion of anxiety-related shortness of breath.

Since current treatment options for COVID-19 disease are limited, we pay particular attention to identifying treatable etiologies of dyspnea including exacerbations of underlying pulmonary and cardiovascular disease and treat the exacerbation as we would have prior to the pandemic.

The typical COVID-19 pattern of a nonspecific viral syndrome – often involving the respiratory system but not infrequently the gastrointestinal system – followed by onset of dyspnea several days later, particularly with precipitous drops in oxygen saturation especially with exertion, are helpful keys to distinguishing COVID-19 from other similar conditions. A nuanced understanding of the typical presentation and natural history of COVID-19 in the ambulatory setting can help determine the appropriate timing of follow-up – patients who have begun to develop dyspnea should be followed closely in the following 72 hours for evidence of worsening dyspnea particularly with exertion – and permit clinicians to more easily distinguish COVID-19 from other common and treatable illnesses.

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