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MAYO CLINIC

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

Pieter A. Cohen, MD; Lara E. Hall, MD; Janice N. John, MHS, MHCDS; and Alison B. Rapoport, MD

From the Departments of Medicine (P.A.C., A.B.R.) and Family Medicine (L.H., J.N.J.), Cambridge Health Alliance, Cambridge, MA; and the Department of Medicine, Harvard Medical School (P.A.C., A.B.R.), Boston, MA.

In March 2020, weeks before the coronavirus disease 2019 (COVID-19) pandemic surge was predicted to arrive in Massachusetts, two of us (J.N.J., L.E.H.) 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, concerns regarding false-negative results and delays of up to 5 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 1000 patients in our COVID-19 clinic, however, we came to suspect that many moderate and severe cases of COVID-19 could 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] However, 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 combinations of mild symptoms, including nasal congestion, cough, sore throat, pleuritic chest pain, diarrhea, abdominal pain, headache, myalgias, back pain, and fatigue have tested positive for SARS-CoV-2. We have also cared for many patients who experienced severe symptoms, including fever, cough, myalgias, and exhaustion, during the initial days of infection. Fever is common, but temperature elevations can be mild, particularly at the outset of illness.[4] One of the only early hints to the diagnosis is loss of smell[5] which many of our patients report losing during the first few days of illness. These initial days of SARS-CoV-2 infection are often indistinguishable from many common illnesses.

Although many patients will recover from their initial symptoms over the course of 2 to 3 weeks, for a sizable proportion of

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patients, their clinical course worsens, with dyspnea setting in typically between day 4 and day 10 of illness. We have also seen some patients in whom dyspnea first develops more than 14 days after the onset of symptoms. In the absense of diagnostic testing, 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. 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 factors to monitor are work of breathing and oxygen saturation. Oxygen saturation often decreases 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] Among our patients, essential workers, particarly recent immigrants from Central America who live in close quarters with multiple people, are at risk of disease progression.

Distinguishing COVID-19 from other serious treatable conditions is essential. Community-acquired pneumonia, especially with atypical organisms such as *Legionella*, may present 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 decrease in oxygen saturation level with exertion is highly suggestive of SARS-CoV-2 infection. In the case of *Pneumocysitis* pneumonia, however, the dyspnea typically develops 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. Whereas 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 10 days after symptoms began. Whereas 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 are found at the onset: with anxiety, onset is often immediately after the first symptoms of infection, whereas 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 dyspnea due to 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 anxiety often describe the sensation of not being able to get enough air into their lungs, whereas with SARS-CoV-2 infection, dyspnea is consistently worse with exertion. Although dizziness might occur in both conditions, it too is more likely to be present at rest with anxiety and with exertion in COVID-19. When a pulse oximeter is available, a normal oxygen saturation level with ambulation helps confirm one's clinical suspicion of anxiety-related shortness of breath.

Because current treatment options for COVID-19 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 before 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 decreases in oxygen saturation level 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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Correspondence: Address to Pieter A. Cohen, MD, 236 Highland Ave, Somerville, MA 02143 (pcohen@challiance.org).

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