VIEWPOINT

A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection

Illness Beyond Acute Infection and Public Health Implications

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Although much of the response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has focused on acute coronavirus disease 2019 (COVID-19) illness, accumulating evidence demonstrates morbidity beyond acute SARS-CoV-2 infection.[1-4] At least 2 other periods of illness appear to be temporally associated with SARS-CoV-2 infection: a rare postacute hyperinflammatory illness and late inflammatory and virological sequelae. These 3 illness periods not only define the temporal course of SARS-CoV-2 infection at the population level but also capture distinct phases of host-viral interaction.

A theoretical framework describing illness periods of SARS-CoV-2 infection (including clinical presentations and timing of onset), their pathophysiological underpinnings, and associated key laboratory findings may contribute to a more inclusive and ordered understanding of the natural history of SARS-CoV-2 infection and enhance research efforts. Within the proposed framework, a patient may experience any combination of these illnesses or may have asymptomatic infection without illness (**Figure**).

> At least 2 other periods of illness appear to be temporally associated with SARS-CoV-2 infection: a rare postacute hyperinflammatory illness and late inflammatory and virological sequelae.

Acute Infection or COVID-19

Acute infection or COVID-19 represents the initial illness period following SARS-CoV-2 infection and is the best characterized of the 3 illness periods. The onset of COVID-19 signs or symptoms (eg, cough, fever, dyspnea) is associated with viral replication and initial host immune response.[5] Asymptomatic SARS-CoV-2 infection may occur in 3% to 67% of infected patients[6] and can be followed by the other 2 illness periods; therefore, symptomatic infection is not a necessary precursor to later illnesses. The duration of acute infection is typically days to weeks.[7] Key laboratory findings include positive test results for SARS-CoV-2 components (ie, positive reverse transcriptase–polymerase chain reaction [RT-PCR] or antigen tests) followed by seroconversion (ie, positive for IgM or IgG) for the majority of patients within 2 weeks following initial symptom onset.[8]

Postacute Hyperinflammatory Illness

A rare multisystem inflammatory illness has been observed in both children and adults following acute SARS-CoV-2 infection.[1,2] Distinct from early inflammation resulting from viral replication and cell death, hyperinflammation can occur in organ systems distinct from those affected during COVID-19 and can begin after host clearance of SARS-CoV-2 infection. The pathophysiology of this illness, termed *multisystem inflammatory syndrome* in children (MIS-C) and in adults (MIS-A), remains under investigation but likely reflects a dysregulated host immune response.[1,2] MIS-C and MIS-A manifest approximately 2 to 5 weeks after onset of SARS-CoV-2 infection.[1,2]

Patients may have prominent cardiovascular and gastrointestinal manifestations as well as dermatological and mucocutaneous manifestations similar to the hyperinflammatory condition Kawasaki disease.[1,2] Laboratory testing may reveal elevated inflammatory markers (eg, C-reactive protein and ferritin levels), coagulopathy (eg, D-dimer), and elevated cardiac markers (eg, troponin level).[1,2] Patients with MIS-C and MIS-A are found to be almost universally antibody positive, but many have negative RT-PCR test results for SARS-CoV-2 infection.[1,2] The extent of MIS-A has not been as well-characterized as MIS-C, likely because adults often have more comorbidities and more severe COVID-19 illness compared with children.[9] The more complex and prolonged course of illness makes it difficult to identify hyperinflammation as a distinct process from acute infection in adults.

Late Inflammatory and Virological Sequelae

Late sequelae have been observed for several infectious diseases, including Lyme disease, syphilis, and Ebola. The etiologies of such late sequelae are not all well characterized, but may reflect organ involvement during the acute infection period, manifestations of a long-term hyperinflammatory state, physical debilitation or psychological sequelae following a long or difficult disease course, or ongoing viral activity associated with a host viral reservoir.

Understanding of late sequelae of SARS-CoV-2 infection is still limited, particularly because early reports have been selected case series without any comparison groups. In one study, 87% of 143 previously hospitalized patients had 1 or more persistent symptoms (including fatigue, dyspnea, joint pain, and chest pain) 60 days after the date of initial COVID-19 symptom onset.[3] These late sequelae do not appear to be necessarily limited to persons requiring hospitalization. However, very limited data are available at the population level about the extent of late sequelae.

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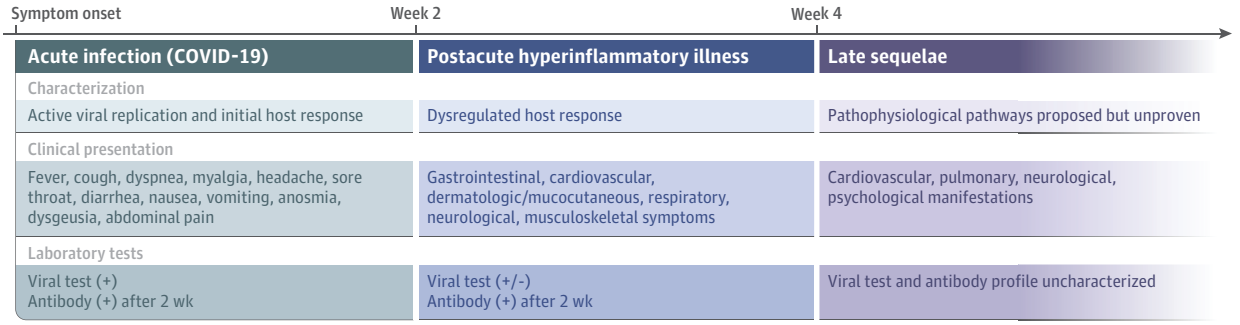
Figure. Proposed Population-Based Framework for Symptomatic SARS-CoV-2 Infection[a]



COVID-19 indicates coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Population-based framework refers to the fact that these illnesses are observed at the population level and not necessarily in any given individual.

Some reports have described late sequelae involving cardiovascular, pulmonary, neurological, and psychological manifestations.[4] The etiology of these late sequelae remains uncertain.

The third illness period in this proposed framework comprises late sequelae of SARS-CoV-2 infection attributable to either an inflammatory or viral host response that occur approximately 4 weeks after initial infection and continue for an as yet uncharacterized duration. Interest in late sequelae continues to increase as numerous reports detailing the plight of patients characterized as SARS-CoV-2 "long haulers" continue to emerge. At present, there is limited information about the underlying pathophysiology, disease duration, or long-term prognosis of affected persons. It is possible that the late sequelae of COVID-19 represent multiple syndromes resulting from distinct pathophysiological processes along the spectrum of disease.

Public Health Significance

This proposed framework will be further refined with accumulating evidence, especially regarding the postacute hyperinflammatory phase and late sequelae. However, this framework may provide a useful approach to understanding the extent of morbidity and mortality from SARS-CoV-2 infection and may have important implications for public health surveillance, clinical research, future treatments, and health services planning. Acute COVID-19 is only a subset of the morbidity and mortality attributable to SARS-CoV-2–associated disease. Until this time, and rightfully so, most efforts have centered on prevention and treatment of acute illness. However, future medical and social interventions must consider the full spectrum of disease due to SARS-CoV-2, the cost and consequences of which extend beyond initial case diagnosis and treatment.

ARTICLE INFORMATION

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