Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COMMENTARY

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Long-COVID: Phase 2 of the COVID-19 Pandemic

Attainment of over 70% coronavirus disease 2019 (COVID-19) vaccination in most areas of the United States has changed the predominant impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from a pandemic of severe acute pulmonary infection in Phase 1 to prolonged debilitating involvement of the brain, cardiovascular system, gastrointestinal system, lungs, and some endocrine organs in Phase 2 (Table).[1-7] In both phases, SARS-CoV-2 must enter normal cells to reproduce and spread to other cells. In Phase 1, pulmonary and immune system cells are invaded first, to the greatest extent and persistently.[8] In Phase 2, there is sustained infection of cells in many organ systems when viral RNA is no longer detectable in blood. SARS-CoV-2-infected immune and other cells are compromised by 2 major viral mechanisms: 1) adoption of viral RNA replication and reduction of host cell RNA translation with consequently diminished host cell production of vital functional proteins, and 2) occupancy of host cell mitochondria with resultant decreases in cellular energy (adenosine triphosphate [ATP]) generation, immune and other resistance to SARS-CoV-2, effective reduction-oxidation homeostasis, and production of cell protective peptides.[1,9,10] Host cells often survive, but their major functions are impaired. In the brain, this may even result in macroscopic structural lesions.[5]

Secretion of type 1 interferon is critical for optimal acute host defense in Phase 1. For several reasons, up to 20% of individuals in the United States are unable to produce type 1 interferon at protective levels or respond to type 1 interferon optimally after SARS-CoV-2 infection and thus, are highly susceptible to severe acute COVID-19.[11] Effective immunity to SARS-CoV-2 through vaccines has decreased the severity of acute COVID-19 in Phase 1, but the risk of developing post-acute sequelae of COVID-19 (PASC) or long COVID in Phase 2 is not clearly related to the severity of acute COVID-19. Perhaps as a result, current preventative and treatment measures for Phase 1 COVID-19 have not appreciably reduced the prevalence or severity of PASC, except for a probable modest reduction in cardiovascular complications associated with prior full vaccination.[12,13] Further, there is as yet no proven treatment for established PASC.

Because all cellular involvement by SARS-CoV-2 is accompanied by inflammation capable of diminishing organ function, it is difficult to separate direct viral effects from those of attendant inflammation. For abnormal cardiac rhythms, however, the evidence favors a causal pathophysiological role of inflammatory cytokines in Phase 2.[14] Eliminating SARS-CoV-2 eventually decreases tissue inflammation, but anti-inflammatory therapy alone has not had striking beneficial effects in PASC. Microvascular disease and microclots, that first were observed with single-photon emission computed tomography (SPECT-CT) scans in lungs of PASC patients,[15] may accompany the inflammation of Phase 2 in multiple organ systems and further diminish organ functions (Table).

Host and viral factors determine the effectiveness of immunity in diminishing SARS-CoV-2 infectivity, intracellular persistence, and evasion of host defenses. As type 1 interferon and neutralizing antibody levels increase acutely in Phase 1, T-cell blood levels and protective functions decrease, in part due to mitochondrial dysfunction.[16] In prolonged Phase 1 COVID-19 and in Phase 2 PASC after vaccination, neutralizing antibody and T-cell blood levels increase and decay in parallel, but T-cell functional activation remains elevated as neutralizing antibody levels decrease.[17,18] In PASC, therefore, T-cell immunity is likely to become progressively more important to host defense for 2 reasons. First, T-cell immunity has a major role in eradicating the widespread intracellular SARS-CoV-2 characteristic of PASC, whereas neutralizing antibody cannot enter cells. Second, lingering intracellular SARS-CoV-2 in PASC rapidly accumulates many mutations typical of dangerous variants of concern, including Omicron,[19] against which neutralizing antibodies have far lower titers.[17] In contrast, T-cell immunity to these variants of concern remains high over time.[17]

Laboratory blood tests can confirm the presence of SARS-CoV-2 in specific tissues.[20] The current strategies of

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Table Phases of the COVID-19 Pandemic

Phase 1: 2019-2021	Phase 2: 2022- ?
Vulnerable population	Extensive vaccination (>70%)
❖ Rapid spread	❖ Milder pulmonary disease
❖ High % severe pulmonary disease	❖ Wider, longer organ system involvement
❖ High % mortality	❖ Long-COVID/PASC: months to years of disability
❖ Facilities & personnel overload	❖ Viral intracellular residence in brain, heart, lungs, GI tract, pancreas
Host immune defects	❖ CNS microvascular disease
❖ Low interferon responses	❖ Mutations in situ
❖ Viral invasion of immune cells	❖ Greater role of T-cell immunity
Initiation of testing, isolation/protection	Re-opening of human interactions
Limited treatments	New treatments
❖ Convalescent plasma	❖ Evolution of vaccines
❖ Monoclonal antibodies	❖ Emerging antiviral drugs
❖ Few drugs - Remdesivir	❖ Nanobodies

CNS = central nervous system; COVID-19 = coronavirus disease 2019; GI = gastrointestinal; PASC = post-acute sequelae of COVID-19.

vaccination alone do not eliminate or even suppress established PASC, in part because antibodies from conventional active or passive immunization do not enter cells to eliminate SARS-CoV-2. Therapeutic emphasis now must be placed on appropriate use of antiviral drugs that enter infected cells and on nanobodies that also enter cells and neutralize SARS-CoV-2.[21-24] These specialized diagnostic and therapeutic approaches will be critical for elimination of PASC and complete suppression of the SARS-CoV-2 pandemic.

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