COVID-19 and the Heart

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ABSTRACT

Infection with the novel coronavirus, SARS-CoV-2, produces a clinical syndrome known as COVID-19. When severe, COVID-19 is a systemic illness characterized by hyperinflammation, cytokine storm and elevations of cardiac injury biomarkers. Here we review what is known about the pathophysiology of COVID-19, its cardiovascular manifestations, and emerging therapeutic prospects. In this rapidly moving field, this review was comprehensive as of April 3, 2020.

Keywords:
cardiovascular disease, myocarditis, coronavirus, cytokine storm, cell therapy, inflammation.

Nonstandard Abbreviations and Acronyms:

ACE: angiotensin-converting enzyme
ACE2: angiotensin-converting enzyme 2
ACS: acute coronary syndromes
AMI: acute myocardial infarction
BNP: brain-type natriuretic peptide
CDCs: cardiosphere-derived cells
CRP: C-reactive protein
COVID-19: 2019 novel coronavirus disease
IL: interleukin
MERS: Middle East respiratory syndrome
MERS-CoV: Middle East respiratory syndrome coronavirus
MSCs: mesenchymal stem cells
RAAS: renin-angiotensin-aldosterone system
SARS: severe acute respiratory syndrome
SARS-CoV: severe acute respiratory syndrome coronavirus
SARS-CoV-2: severe acute respiratory syndrome novel coronavirus
TnI: troponin I

INTRODUCTION

The number of patients with the 2019 novel coronavirus disease (COVID-19) continues to rise, with more than one million confirmed cases worldwide.[1] Based almost exclusively on data from China, where the pandemic originated, cardiac injury appears to be a prominent feature of the disease, occurring in 20-30% of hospitalized patients and contributing to 40% of deaths.[2-4] Scholarship on COVID-19 is rapidly evolving: the cumulative number of PubMed citations involving both terms "COVID" and "heart" increased from none on February 20th to n=61 by April 3, 2020, while ~2000 publications appeared with the term "COVID" alone in the first three months of the calendar year. Many more papers are listed in non-refereed archives (e.g., medRxiv and bioRxiv).

Compared to other major viral outbreaks in contemporary history, including severe acute respiratory syndrome (SARS) of 2002-2003, COVID-19 appears to have a lower case-fatality rate. The symptomatic case fatality risk is 1.4% but increases substantially after 60 years of age. Interestingly, the relative susceptibility to symptomatic infection also increases with age, raising questions about underlying biology of host responses in relation to age.[5] Despite the relatively low case fatality risk, however, the basic reproduction number (a measure of transmissibility) is around

2.0-2.5, suggesting that it spreads more easily.[6] Coupled with an impressive capacity for asymptomatic transmission, the SARS novel coronavirus (SARS-CoV-2) has ideal attributes for pandemic spread.[7, 8]

In this Review, we discuss cardiac involvement in the context of SARS-CoV-2 immunology, the speculated role of angiotensin converting enzyme 2, and emerging therapeutic strategies, which now include cell-based approaches.

Immune Over-Reaction Kills.

Acute disease progression can be divided into three distinct phases: an early infection phase, a pulmonary phase, and a severe hyperinflammation phase (Figure 1).[9-11] In any given patient, however, there can be significant overlap among the phases. Although most cases are mild or asymptomatic (81%)[12], this paradigm of disease progression in critically-ill COVID-19 patients is heuristically instructive in highlighting the role of inflammation and secondary organ involvement. During the early infection phase, the virus infiltrates the lung parenchyma and begins to proliferate. This stage is characterized by mild constitutional symptoms and marks the initial response by innate immunity, namely monocytes and macrophages. Collateral tissue injury and the inflammatory processes that follow—vasodilation, endothelial permeability, leukocyte recruitment—lead to further pulmonary damage, hypoxemia and cardiovascular stress. In a subset of patients, the host inflammatory response continues to amplify (even with diminishing viral loads) and results in systemic inflammation.[11, 13] This systemic toxicity, in turn, has the potential to injure distant organs. Reports of myocarditis in COVID-19 without evidence of direct viral infiltration implicate the heart as one such target of systemic inflammation (Figure 2).[14]

Within this framework of acute disease progression, lymphocytopenia is a prominent feature and is associated with adverse outcomes. A higher proportion of non-survivors and critically ill COVID-19 patients exhibit progressive lymphocytopenia (Figure 3A). Despite diminished lymphocyte counts, however, patients with severe disease eventually develop higher white blood cell and neutrophil counts.[3, 15-17] This suggests a high vulnerability of lymphocytes to viral infection and destruction. Autopsy studies from the SARS epidemic, caused by the nearly identical SARS-CoV, revealed not only the capacity for direct leukocyte infection but also a relative predilection for lymphocytes. Over 50% of lymphocytes harbored viral particles by electron microscopy, and most of these were T cells (Figure 3B). Both $CD4^+$ and $CD8^+$ T cells were reduced and remained low until convalescence (Figure 3C).[18] Furthermore, secondary lymphoid organs contained decreased numbers of lymphocytes, suggesting that sequestration did not account for lymphocytopenia. Patients infected with SARS-CoV-2 likewise exhibit lower levels of T lymphocytes, with decreases in both helper and regulatory T cells.[19] The decrease in regulatory T cells is especially notable, given their critical role in immune homeostasis and prevention of excessive inflammation after infection.[10, 20-22]

Exaggerated systemic inflammation, or cytokine storm, may correlate with lymphocytopenia and is a hallmark of severe disease.[23] Systemic inflammation represents an advanced stage of the acute illness (the third phase in Figure 1), characterized by multiple organ failure and elevation of key inflammatory markers.[9] Based on clinical data, these inflammatory markers include interleukin (IL)-6, IL-2, IL-7, tumor necrosis factor (TNF)-α, interferon-γ inducible protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP) 1-α, granulocyte-colony stimulating factor (G-CSF), C-reactive protein (CRP), procalcitonin, and ferritin.[3, 15-17, 23] Following a viral infection, these cytokines activate pathways that lead to immune cell differentiation, trafficking of leukocytes to sites of infection, and expansion of hematopoietic progenitor cells.[24] These biomarkers are not just indicators of

inflammation but also are associated with high mortality. In retrospective clinical series, non-survivors exhibited higher levels of IL-6, ferritin (Figure 4A) and CRP (Figure 4B). [3, 16] Although inflammation starts and propagates at the organ of initial injury (i.e., lungs), the amplified inflammatory response can have deleterious bystander effects on other organs, including the heart. Consistent with this notion, biomarkers of cardiac injury and electrocardiographic abnormalities correlate with elevated inflammatory markers.[4, 25] This represents an *indirect* mechanism of cardiac injury. There are hypotheses, however, that implicate *direct* myocardial injury, as well.

The Role of Angiotensin-Converting Enzyme 2 in COVID-19.

Angiotensin-converting enzyme 2 (ACE2) is a carboxypeptidase that converts angiotensin II into angiotensin-(1-7). This enzyme is homologous to angiotensin-converting enzyme (ACE) but serves a counterbalancing role in the renin-angiotensin-aldosterone system (RAAS).[26-28] Beyond its function in cardiovascular homeostasis, ACE2 is also a functional receptor and a portal of entry for both SARS-CoV and SARS-CoV-2.[29-31] The reader is referred elsewhere for an extensive review of this crucial link in the pathogenesis and pathophysiology of COVID-19.[32] ACE2 is expressed in multiple tissues, including lungs, heart, and kidneys.[28, 33] In animal models, ACE2 expression in the heart is an essential regulator of function, with ACE2 knockout mice developing severe left ventricular dysfunction.[34] SARS-CoV infection appears to downregulate ACE2, which may contribute to myocardial dysfunction.[35] Thus, the link between SARS-CoV and ACE2 provides one theoretical mechanism for cardiac dysfunction in COVID-19: ACE2 downregulation leads to cardiac dysfunction. In addition, the relationship between viral entry and ACE2 forms the basis for the controversy surrounding the use of RAAS antagonists, which increase ACE2 expression in animal studies and, therefore, can theoretically increase susceptibility to infection. But even the directionality of the effects is debated: higher ACE2 levels may be protective, by providing a reservoir of receptors to offset those lost in the course of infection.[36, 37] However, there is, as yet, no convincing, corollary data in humans relating to the virus of interest, SARS-CoV-2.

Cardiac Involvement.

Cardiac involvement, at least at the level of biomarker elevations, is a prominent feature in COVID-19 and is associated with a worse prognosis.[2, 3, 15-17] For example, patients with adverse outcomes, including ICU admission and mortality, had significantly higher levels of cardiac troponin I (TnI) (Figure 4B,C).[3, 16] Brain-type natriuretic peptide (BNP) levels were also elevated among ICU admissions in Washington, and appeared more universal than troponin elevations.[38] Furthermore, among causes of death in a Wuhan cohort, myocardial damage and heart failure contributed to 40% of deaths, either exclusively or in conjunction with respiratory failure.[3] In an adjusted Cox regression model, patients with elevated circulating biomarkers of cardiac injury were at significantly higher risk of death.[2] Surprisingly, the mortality risk associated with acute cardiac injury was more significant than age, diabetes, chronic pulmonary disease, or prior history of cardiovascular disease.[2, 4] Thus, cardiac involvement is both prevalent and, apparently, prognostic in COVID-19. Nevertheless, little is known regarding the incidence of genuine clinical manifestations of heart disease; biomarker elevations may simply reflect systemic illness in a large fraction of critically-ill COVID-19 patients.

The mechanisms of cardiac injury are not well established but likely involve increased cardiac stress due to respiratory failure and hypoxemia, direct myocardial infection by SARS-CoV-2, indirect injury from the systemic inflammatory response, or a combination of all three factors (Figure 2). Case reports of myocarditis in COVID-19 provide evidence for cardiac inflammation but do not illuminate the mechanism. Autopsies show inflammatory infiltrates composed of

macrophages and, to a lesser extent, $CD4^+$ T cells.[14, 39] These mononuclear infiltrates are associated with regions of cardiomyocyte necrosis, which, by Dallas Criteria, defines myocarditis.[40, 41] Thus far, however, there are no data demonstrating the presence of SARS-CoV-2 within myocardial tissue. Postmortem real-time PCR analyses of heart tissue from the SARS epidemic, however, detected the viral genome in 35% of patients (n=7/20) who died from SARS. Of note, these hearts also had decreased levels of ACE2 and increased hypertrophy.[35] Taken together, it remains unclear how much of the cardiac injury is attributable to direct viral infection versus indirect systemic toxicity. Furthermore, it is unclear which cell populations within the myocardium are most vulnerable to infection and/or systemic inflammation. ACE2 expression levels may give a hint, but again the implications of such differences are debatable. Myocardial pericytes, which play an important role in maintaining endothelial function, express ACE2 abundantly.[42] Dysfunction in cardiac pericytes and endothelial cells, either due to direct infection or global inflammation, can lead to disruption in the coronary microcirculation with downstream ischemic consequences, but the relationship to COVID-19 is purely conjectural.

Finally, there are insufficient data to determine whether myocarditis in COVID-19 more commonly causes heart failure with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF). Although there are isolated COVID-19 reports of depressed ventricular function, the majority of patients with uncomplicated lymphocytic myocarditis present with normal heart function.[43-46] Consistent with the possibility that HFpEF may be more common, a case report from Wuhan highlights the coexistence of elevated TnI and BNP in a critically-ill COVID-19 patient with an echocardiographic ejection fraction of 60%.[47] Given the difficulty of performing echocardiography under strict isolation while wearing personal protective equipment, and the associated risk to staff, the exact prevalence and nature of cardiac dysfunction in COVID-19 may never be fully apparent.

Other facets of cardiac involvement include blood pressure abnormalities and arrhythmias. In a Wuhan cohort, a higher proportion of critically ill patients and non-survivors had elevated blood pressure, which is counterintuitive in a critically ill, vasoplegic population.[3, 17] Whether this hypertension is simply a reaction to the illness, a predisposing factor to the illness, or a phenomenon related to potential derangements in ACE2 expression cannot be ascertained from the retrospective data. It is also important to note that in different cohorts, including the critically ill patients in Washington State, the patients were hypotensive and required vasopressor support, as is typical for patients with severe infectious diseases.[48] In addition to blood pressure abnormalities, patients can also develop arrhythmias, ranging from tachycardia and bradycardia to asystole. Based on epidemiological data, palpitations are present in 7.3% of patients, and a significantly higher proportion of critically ill patients develop arrhythmias, though these have not yet been characterized.[15, 49] Arrhythmias in this patient population can arise secondary to hypoxemia, metabolic derangements, systemic inflammation, or myocarditis.

Finally, acute coronary syndromes (ACS) and acute myocardial infarction (AMI) can occur in COVID-19 patients, but the incidence of such events is unclear. In principle, risk for ACS in afflicted patients may be increased due to heightened thrombotic proclivity, as evidenced by significantly elevated D-dimer levels.[15-17] Underlying this risk are known predisposing factors related to inflammation: endothelial and smooth muscle cell activation; macrophage activation and tissue factor expression in atheromatous plaque; and platelet activation with further elaboration of inflammatory mediators.[50] Clinical studies on prior epidemics corroborate these observations by showing a strong association between viral respiratory infections and AMI (incidence ratio for AMI within 7 days of infection: 2.8 to 10.1).[51] Although robust data on the scope of AMI in COVID-19 are not available yet, AMI did contribute to in-hospital mortality in the SARS epidemic.[13] Given the risks incurred by transporting infected patients and subjecting them to percutaneous

intervention, some centers are adjusting their ACS protocols and treatment paradigms, with increasing consideration given to thrombolytic therapy.[52, 53] Finally, the symptoms of infection and the high prevalence of non-ischemic cardiac injury can masquerade as ACS (including electrocardiographic abnormalities, troponin elevations and chest pain); therefore a high index of suspicion for alternative diagnosis is necessary.[46]

Therapeutics.

The progression of COVID-19 involves distinct but overlapping pathophysiological phases (Figure 1). Appreciation of these phases may allow informed deployment of tailored therapy. For example, immunosuppressive regimens are likely most beneficial during the hyperinflammation phase, rather than the early infection phase when intact immunity may be critical for pathogen eradication. Thus, the use of the agents discussed below must be considered in the context of disease progression, although little phase-specific distinction has been made so far in the literature. Table 1 summarizes the properties of various agents under investigation for the treatment of COVID-19.

Antiviral and Antimalarial Agents: Lopinavir and ritonavir are HIV protease inhibitors that demonstrated antiviral effects *in vitro* against SARS-CoV (Figure 5A) and decreased viral loads in non-human primates infected with MERS-CoV (Figure 5B).[54-56] An open-label randomized controlled trial, however, did not show efficacy in COVID-19 patients (Figure 5C).[57] Remdesivir, a nucleoside analogue initially developed for Ebola, was also effective against SARS/MERS-CoV *in vitro* and in murine and non-human primate models.[58, 59] Importantly, remdesivir was also able to inhibit SARS-CoV-2 *in vitro*.[60] Thus far, however, the only clinical evidence of remdesivir efficacy in COVID-19 is a case report.[61] Ribavirin showed similar therapeutic potential in a preclinical study with MERS-CoV-infected rhesus macaques, but these findings have not been translated to COVID-19.[62] Finally, favipiravir was recently tested in an open-label randomized trial and showed faster resolution of fever and cough but similar rates of respiratory failure compared to the control group receiving umifenovir.[63] These latter findings have not undergone peer-review yet, and the study design has a number of deficiencies. Another agent that has garnered attention in the media is hydroxychloroquine. Both chloroquine and hydroxychloroquine showed inhibitory effects against SARS-CoV-2 *in vitro*.[60, 64] Hydroxychloroquine (with or without adjunctive azithromycin) has also been claimed to be effective in COVID-19 patients, but this study had several major shortcomings.[65] Figure 5D shows a timeline of the work available to date on antimalarials and COVID-19. Although more recent trials involving hydroxychloroquine improved in design and execution, the evidence for efficacy remains tentative; further evaluation will be necessary to justify the routine use of hydroxychloroquine in COVID-19.[66] Finally, serine protease inhibitors that target viral entry also represent a potential therapy. SARS-CoV-2 gains entry into the cell through a process that requires priming of the S protein by the host serine protease TMPRSS2, which can be inhibited by a clinically available serine protease inhibitor.[67] Future clinical trials will provide answers about the feasibility and efficacy of this and other treatments in COVID-19.

It is important to note that the antiviral and antimalarial agents above have potential cardiac toxicities, including conduction abnormalities and long QT syndrome, necessitating careful electrocardiographic monitoring.[68] Therefore, the off-label use of these agents, while rampant in the real world, must be carefully considered in the context of demonstrated risk but uncertain benefit.

***Immunoglobulins and anti-IL6 antibodies*:** The rationale behind immunoglobulin use relies on two mechanisms: viral neutralization and immunomodulation. One intriguing application of the former mechanism is the use of convalescent serum or plasma. In this application, serum is collected from patients who recover from illness, screened for viral-neutralizing antibodies, and administered in a prophylactic or therapeutic manner.[69] This passive antibody therapy is believed to neutralize the SARS-CoV-2 virus, thereby attenuating disease severity, but will likely have the greatest effect if administered early.[69, 70] A recent case series showed that transfusion of convalescent plasma into critically ill COVID-19 patients improved clinical outcomes, but these findings will require validation in prospective clinical trials.[71] Unlike convalescent plasma, intravenous immune globulin (IVIG) therapy relies on polyclonal antibodies from a pool of healthy donors. IVIG has pleiotropic effects that culminate in suppression of inflammation, and therefore this therapy can potentially alleviate disease severity in the hyperinflammation phase. Case reports support this hypothesis, but more robust evidence is needed to confirm these findings.[72] Likewise, there is good reason to wonder if COVID-19 patients with cytokine storm may benefit from monoclonal antibodies targeting IL-6 or IL-6 receptor, which have been successful in attenuating the sequelae of inflammation in transplant patients, but very limited clinical data support this conjecture.[73, 74]

Corticosteroids: Corticosteroid use was common during the SARS and MERS epidemics and continues today with COVID-19 on an ad hoc basis, despite lack of clinical evidence of efficacy. In severe cases of the disease, characterized by hyperinflammation, there is a theoretical rationale for corticosteroid use. Additionally, corticosteroid use was associated with a lower incidence of myocardial infarction among patients hospitalized for pneumonia.[75] This observation harkens back to the discussed relationship between inflammation and thrombotic proclivity. Randomized trials, meta-analyses, and case-control studies from prior viral epidemics, however, demonstrated no survival benefit.[76]

Cell-Based Therapies.

In the field of heart disease, clinical studies with cell therapy began nearly two decades ago, and have involved skeletal myoblasts, bone marrow mononuclear cells, mesenchymal stem cells (MSCs), mesenchymal precursor cells, $CD34^+$ cells, cardiopoietic cells, and cardiosphere-derived cells (CDCs). While such trials have been generally disappointing in achieving myocardial regeneration, extensive preclinical studies, and some clinical findings, support the notion that cell therapy can attenuate inflammation, which may be attractive in COVID-19.[77]

MSCs are somatic progenitor cells that possess immunomodulatory properties.[78] Two recent studies investigated the effects of MSCs in COVID-19. The first study enrolled seven patients and demonstrated improvements in pulmonary function and peripheral lymphocyte counts after MSC infusion. Of note, the majority of patients (6/7) were not critically ill, and with a small control group (n=3) it is difficult to conclude whether clinical improvement was part of the natural course or treatment effect.[79] The second study is a case report involving a 65-year-old female who received umbilical cord MSCs[80] superimposed on other therapies, which included corticosteroids, lopinavir-ritonavir, IFN-α, oseltamivir, immunoglobulin, and thymosin α1. Thus, little conclusion can be drawn about the efficacy of MSCs in this report. Additional studies are needed to further assess the efficacy of MSCs.

CDCs are stromal progenitor cells that can be isolated from human heart tissue through well-specified culture techniques (Figure 6A).[81] CDCs have been tested in >200 patients in clinical trials for myocardial infarction, heart failure with reduced and preserved ejection fraction, Duchenne muscular dystrophy, and pulmonary hypertension (Figure 6B), as well as hypoplastic

left ventricle. The trials which have reported results all revealed disease-modifying bioactivity, albeit to variable degrees.[77] CDCs exert their effects in a paracrine manner by secreting exosomes, which have anti-inflammatory and immunomodulatory properties.[82] Within the framework of SARS-CoV-2 pathogenesis, multiple pathways known to be CDC-sensitive may serve as therapeutic targets; Figure 6C shows that these targets include proinflammatory pathways (TNF-α, IFN-γ, IL-1β, IL-6) and anti-inflammatory pathways (regulatory T cells, IL-10) that have been explored in animal models of myocardial ischemia, myocarditis, muscular dystrophy, heart failure with preserved ejection fraction, non-ischemic dilated cardiomyopathy, and pulmonary hypertension.[83-89] The salutary effects in these models, along with the immunomodulatory properties of CDCs, motivated the **C**dc**S** for **C**ytokine **S**torm in **C**ovid **S**yndrome Trial: **(CS)^3**, which has already enrolled several confirmed COVID-19 patients who are critically ill and show signs of lymphocytopenia and cytokine storm. Among exploratory outcomes are mortality, length of stay in intensive care, duration of ventilatory support, and indices of cardiac and immune function. This trial, and studies exploring other cell types, will hopefully provide further insight into the potential utility of cell-based therapies for COVID-19.

Long-term sequelae of SARS-CoV-2 infection.

Cardiovascular complications are possible even after recovery from illness. Figure 7 depicts schematically the concept that, once the acute phase of illness has resolved, longer-term complications may arise in the convalescent and chronic phases of disease, long after viral clearance has been achieved. COVID-19 is a nascent pandemic and, therefore, long-term sequelae are unknown, but there are reports of complications which occur soon after resolution of the acute symptoms. A case report from Italy describes fulminant myocarditis in a convalescent patient one week after her respiratory symptoms resolved.[46] This suggests that background inflammation can persist and evolve silently, manifesting later in an insidious manner. Even after apparently-complete recovery, however, there may be chronic sequelae. The previous SARS epidemic is instructive because sufficient time has elapsed for long-term follow-up. A substantial proportion of survivors from the epidemic developed avascular necrosis, pulmonary fibrosis, and dyslipidemia.[90-92] The latter manifestations are particularly important as they represent cardiovascular risk factors. In addition, hospitalization for pneumonia has been associated with increased short- and long-term risk for cardiovascular disease, and this is especially true if there are cardiac complications during the index hospitalization.[93, 94] Thus, cardiac involvement may persist long after resolution of the acute illness. Much remains to be learned here. In this continuously changing field, this review was comprehensive as of April 3, 2020, but the discussion will continue to evolve with the rapid, daily accumulation of new knowledge—an inspiring and immensely humbling prospect.

Conclusions.

The COVID-19 pandemic has motivated an explosion of new research, which is already providing key insights into the pathogenesis of the disease. Nevertheless, many questions remain unanswered. Lymphocytopenia, hyperinflammation, and cardiac involvement are all prominent features of the disease and have prognostic value, but the mechanistic links among these phenomena are ill-defined. Similarly, despite the rapidly growing number of clinical trials, no definitive therapies (other than supportive care) are available at this time. New therapeutic paradigms, however, are beginning to emerge, and with rigorous investigation will ultimately advance our understanding and treatment of the disease. Even after COVID-19 has become a distant memory, the lessons learned during this uncertain time will likely inform the assessment and therapeutics of other syndromes of hyperinflammation affecting the heart and vasculature.

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FIGURE LEGENDS

Figure 1: Progression of the acute disease in COVID-19. The disease progression over time is divided into three pathological phases: an early infection phase, a pulmonary phase, and a severe hyperinflammation phase. The early infection phase is characterized by viral infiltration and replication. Lymphocytopenia is a key laboratory finding at this stage. The disease progresses into the pulmonary phase, characterized by respiratory compromise and abnormal chest imaging. An exaggerated inflammatory response driven by the host immunity defines the hyperinflammation phase. Inflammatory markers are elevated at this stage, and secondary organ damage becomes apparent. The present schematic depicts only the acute phase of illness (cf. Figure 7). Adapted from References 9, 10.

Figure 2: Proposed mechanisms of cardiac injury with clinical sequelae. Cardiac injury can result via direct or indirect mechanisms. The direct mechanism involves viral infiltration into myocardial tissue, resulting in cardiomyocyte death and inflammation. Indirect mechanisms include cardiac stress due to respiratory failure and hypoxemia, and cardiac inflammation secondary to severe systemic hyperinflammation. Biomarkers (cardiac troponin I and brain-type natriuretic peptide), arrhythmias, myocardial infarction, and heart failure are manifestations of myocardial injury.

Figure 3. Lymphocytopenia and T cell destruction. (A) Progressive lymphocytopenia in COVID-19 patients, with more profound depletion in non-survivors. Reproduced from Reference 16. (B) Electron micrograph demonstrating viral inclusion bodies within a circulating T lymphocyte in patients with SARS-CoV on the left. Bar, 2 μm. Insert: higher power image showing a group of SARS coronavirus-like particles. Bar, 0.2 μm. On right, lymphocyte with three coronavirus-like particles (white arrows). Bar 0.5 μm. Insert: higher power image of the membrane region showing entrance of the viral particle. Bar, 0.1 μm. Reproduced from Reference 18. (C) Lymphocyte counts for $CD3^+$, $CD4^+$, and $CD8^+$ T cells in patients with confirmed SARS and non-SARS controls (n=15/group). Adapted from Reference 18.

Figure 4. Inflammatory markers in survivors and non-survivors with COVID-19
(A) Levels of IL-6 (left) and serum ferritin (right) in survivors (n=137) and non-survivors (n=54). Reproduced from Reference 16. (B) Levels of cardiac troponin, C-reactive protein, and interleukin-6 in patients who died (n=68) and patients who were discharged (n=82). Adapted from Reference 3. (C) Levels of high-sensitivity cardiac troponin I in survivors (n=137) and non-survivors (n=54). Reproduced from Reference 16.

Figure 5. Preclinical and clinical studies showing efficacy of antiviral regimens
(A) *In vitro* antiviral susceptibility test demonstrating dose dependent inhibition of SARS-CoV after 48 hours of incubation with lopinavir. Adapted from Reference 55. (B) Viral loads at necropsy in common marmosets infected with MERS-CoV (n=3/group). Student's *t* test was used. Data are mean ± SD. Reproduced from Reference 54. (C) Left: time to clinical improvement in lopinavir-ritonavir group (n=99) and control group (n=100); right: SARS-CoV-2 viral RNA loads assessed by quantitative PCR in lopinavir-ritonavir and control groups. Bars, 95% confidence intervals. Reproduced from Reference 57. (D) Timeline representing the progression of preclinical and clinical studies involving hydroxychloroquine (HCQ), starting with *in vitro* studies, and progressing through non-randomized clinical series and randomized clinical trials.[60, 65, 66, 97, 98]

Figure 6. Cardiosphere-derived cells and potential therapeutic targets in COVID-19
(A) Schematic for tissue processing and culture methods to generate cardiosphere-derived cells (CDCs). Adapted from Reference 77. (B) Mechanisms of action underlying CDCs' therapeutic

effects, and clinical trials using CDCs. (C) CDC-sensitive therapeutic targets in COVID-19 pathogenesis, which involves activation of macrophages, effector T cells, and production of pro-inflammatory cytokines and chemokines.

Figure 7: Long-term sequelae of COVID-19

After resolution of the acute illness (cf. Fig. 1), prior infection with SARS-CoV-2 may result in persistent manifestation of disease. The schematic depicts the concept of progression over time divided into three phases: acute phase, convalescent and chronic. The times on the X-axis are approximate. Assuming clearance of the SARS-CoV-2 virus in the acute phase, host response likely shapes the manifestations of disease in the convalescent and chronic phases. Disease manifestations remain somewhat conjectural; those listed here are described in case reports, or in the long-term aftereffects of SARS-CoV or MERS-CoV infection.

Table 1. Therapeutic Strategies for COVID-19

Therapy	Rationale for COVID-19	Clinical Evidence in COVID-19
Antimicrobials		
Lopinavir-ritonavir	Inhibits SARS-CoV *in vitro*, improves clinical outcomes in common marmoset with MERS-CoV [54, 55]	No benefit in RCT[57]
Remdesivir	Preclinical efficacy with SARS/MERS-CoV, and SARS-CoV-2 [58-60]	Case report (n=1)[61]
Ribavirin (± IFN)	Improves outcome in rhesus macaques with MERS-CoV[62]; inhibits MERS-CoV *in vitro* [95]	None
Favipiravir	Inhibits SARS-CoV-2 *in vitro* [60]	RCT: improved fever but not respiratory failure[63]
(Hydroxy)chloroquine	Inhibits SARS-CoV-2 *in vitro* [60, 64]	Nonrandomized trial: decreased viral load, no clinical outcomes data[65]
Corticosteroids	Immunosuppressive effect in inflammatory syndromes	None
Immunoglobulin/Antibody-Based Therapies		
Intravenous immunoglobulin	Established immunomodulatory effects in autoimmune and inflammatory syndromes	Case report (n=3)[72]
Convalescent plasma	Passive antibody immunity with capacity to neutralize the virus	Case series showed improved clinical course[71]
IL-6(R) monoclonal antibodies	Immunomodulation for transplantation and immune-checkpoint inhibitor side effects[73, 96]	Case series showed respiratory improvement[74]
Cell-Based Therapies		
Mesenchymal stem cells	Known immunomodulatory properties	Single-arm study (n=7), showed improvement in symptoms, pulmonary function[79] Case report (n=1)[80]
Cardiosphere-derived cells	Known immunomodulatory and cardioprotective properties[83-89]	CS cubed trial currently enrolling

COVID-19: coronavirus disease 2019, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, IFN: interferon, RCT: randomized controlled trial

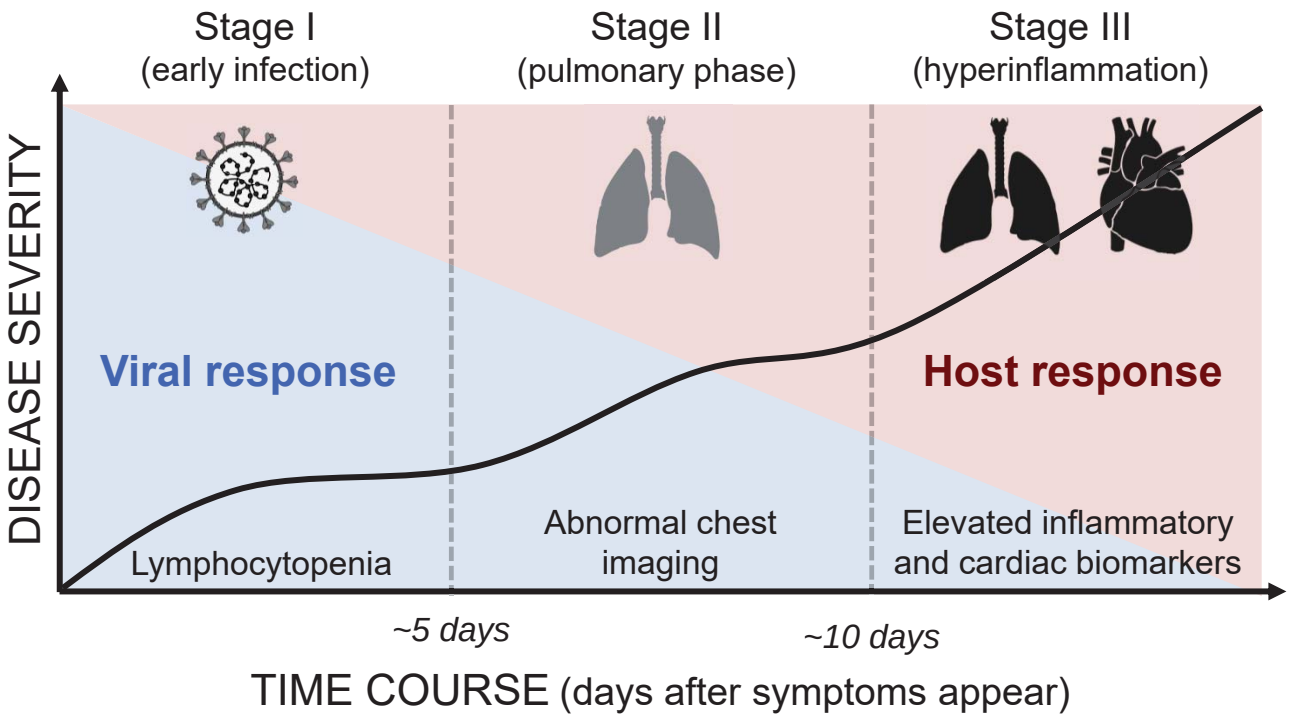

FIGURE 2