Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome

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Coronavirus Disease 2019 (COVID-19) is a rapidly expanding global pandemic due to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) resulting in significant morbidity and mortality. A substantial minority of patients hospitalized develop an Acute COVID-19 Cardiovascular Syndrome (ACovCS) that can manifest with a variety of clinical presentations, but often presents as an acute cardiac injury with cardiomyopathy, ventricular arrhythmias and hemodynamic instability in the absence of obstructive coronary artery disease. The etiology of this injury is uncertain, but is suspected to be related to myocarditis, microvascular injury, pericytes leading to viral myocarditis. Systemically elevated cytokines are also known to be cardiotoxic and have the potential to result in profound myocardial injury. Prior experience with Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) has helped expedite theevaluation of several promising therapies including anti-viral agents, interleukin-6 inhibitors, and convalescent serum. Management of ACovCS should involve a multidisciplinary team including intensive care specialists, infectious disease specialists and cardiologists. Priorities for managing ACovCS include balancing the goals of minimizing healthcare staff exposure for testing that will not change clinical management with early recognition of the syndrome at a time point where intervention may be most effective. The aim of this paper is to review the best available data on ACovCS epidemiology, pathogenesis, diagnosis and treatment.

Treatment of Acute COVID-19 Cardiovascular Syndrome

There are no comprehensive expert recommendations and limited data from high quality studies to inform our clinical decision making for the pharmacotherapy of ACovCS. Since most small case series and studies of viral myocarditis in general involve fulminant and otherwise complicated presentations, there is significant publication bias in the literature. Published experiences of COVID-19 associated myocardial injury is even more limited, including retrospective small case series and/or individual case reports. As such, the best practices for treating the acute myocardial injury in ACovCS currently need to be extrapolated from prior non-COVID-19 experiences and the available, limited quality COVID-19 data. In general, treatment of ACovCS should be completed with a multidisciplinary team including infectious disease consultation to help guide therapy selection. Several experimental therapies attempting to limit SARS-CoV-2 replication or the immune response have been proposed with multiple clinical trials currently underway. Currently there are no therapies with rigorous clinically supported efficacy for COVID-19 in general, or specifically for ACovCS. If possible, enrollment in on-going clinical trials is encouraged.

Hydroxychloroquine is a proposed treatment for COVID-19 on the basis of in *vitro* testing and a small open-label study with significant methodological limitations. The clinical study enrolled 42 patients with 26 patients receiving hydroxychloroquine compared to 16 controls. Only 36 patients were included the analysis, as 6 (23%) of the hydroxychloroquine treated patients were lost to follow-up. The study authors concluded that hydroxychloroquine had a significant effect and led to rapid SARS-CoV-2 clearance. This conclusion appears overstated based upon the study design and results, and we believe further studies of hydroxychloroquine, including its impact on ACovCS, are required.

Antiviral therapies may have a role in the treatment of ACovCS. The use of lopinavir/ritonavir for severe COVID-19 was tested prospectively in 199 patients, but unfortunately did not lead to a significant reduction in viral-load or symptomatic improvement. Remdesivir has also been proposed as an anti-viral therapy after originally being developed for Ebola and the Marburg virus. Subsequent investigation demonstrated significant reduction of viral replication and symptoms in a mouse model infected with SARS-CoV-1. Additional *in vitro* testing of a human cell line demonstrated markedly reduced SARS-CoV-2 activity. This led to compassionate use of remdesivir in COVID-19 patients, an effort which was eventually suspended with initiation of currently enrolling prospective clinical trials.

Both hydroxychloroquine and antiviral therapies may increase the risk for torsades de pointes via QTc prolongation. This risk may be increased in ACovCS if there are abnormalities of cardiac structure or function

(e.g. left ventricular hypertrophy or reduced ejection fraction), concomitant ventricular arrhythmias or a prolonged QT interval at baseline.

Immunosuppression for myocardial injury in ACovCS has been proposed as a treatment option; however, prior experiences with broad immunosuppression for acute myocarditis historically have not been favorable. In the Myocarditis Treatment Trial, no significant difference was seen in LVEF or survival between those treated with cyclosporine/prednisone, azathioprine/prednisone or placebo in patients with myocarditis in the pre-COVID era. While there were several limitations of the trial, these results do not support widespread use of immunosuppressive therapies for myocarditis. A systematic Cochrane review evaluated the efficacy of steroids for acute viral myocarditis in 8 randomized controlled trials with a total of 719 patients in the pre-COVID era. They concluded that glucocorticoid therapy did not reduce the composite end-point of mortality or heart transplant. Steroid use in severe COVID-19 appears common in reports, and use is numerically higher in non-survivors, although that observation is likely confounded by indication for steroid initiation. Given the concern that steroids may prolong SARS-COV-2 viral persistence, corticosteroid treatment should not be routine, but rather may be considered salvage therapy with multidisciplinary input in select cases with hemodynamically unstable patients. As discussed above, activation appears to be a prominent feature of severe COVID-19 illness and ACovCS with marked elevations of IL-6 and other inflammatory markers. Sarilumab, siltuximab and tocilizumab are IL-6 inhibitors that have potential utility in ACovCS and severe COVID-19. Tocilizumab is FDA-approved to manage cytokine release syndrome due to CAR-T cell therapy and is being investigated for pneumonitis induced by immune checkpoint inhibitors. Trials with sarilumab, siltuximab and tocilizumab are underway in patients with COVID-19, and will provide additional information on therapeutic efficacy and safety and impact on ACovCS. In the interim, these agents can be considered for -by-case basis with multidisciplinary input. Given the known association between myocarditis and auto-antibodies, intravenous immunoglobulin (IVIG) is theorized as a possible treatment for viral-associated myocarditis.

However, in a well conducted study in the pre-COVID era, IVIG did not improve LVEF or event-free survival at 1-year follow-up. This study highlighted the lack of high-quality evidence for the routine use of IVIG to treat with idiopathic dilated cardiomyopathy or myocarditis, although the treatment appeared safe. Use of 1 g/kg IVIG daily for two days can be considered in select cases for hemodynamically unstable patients due to suspected fulminant myocarditis as salvage therapy with multidisciplinary input. However, it is important to note this is an extremely limited resource and should be reserved for patients with high clinical suspicion of cardiomyopathy due to myocarditis rather than cytokine storm or stress-induced cardiomyopathy.

More focused antibody therapy using convalescent plasma from recovered COVID-19 patients has been approved recently by the Food and Drug Administration. A recent report described treatment of 5 critically ill patients with convalescent plasma containing a SARS-CoV-2– specific antibody (IgG) obtained from COVID-19 survivors. In this uncontrolled case series, they reported an improved clinical status, an observation which merits further clinical investigation.

If myocardial injury is diagnosed clinically and the patient recovers from COVID-19, similar to historical expert opinion recommendations for non-COVID myocarditis, abstinence from competitive sports or aerobic activity would be reasonable for a period of 3-6 months until resolution of myocardial inflammation by cardiac MRI and/or normalization of troponin. This recommendation is based on experimental animal models and several retrospective observational studies. The initiation of guideline-directed medical therapy (GDMT) may be considered for all patients with suspected myocarditis and reduced systolic function in accordance with the most recent guidelines for the management of heart failure after a period of clinical stability and improvement such that individuals are preparing for discharge. We advise delaying GDMT until that later time point given that respiratory status can deteriorate rapidly earlier in the illness and require intubation leading to hypotension.

Finally, in select cases with refractory shock or ventricular arrhythmias due to ACovCS, mechanical support can be considered if available at the treating facility. Case reports have described successful rescue of patients with cardiogenic shock with use of veno-arterial (VA), and veno-arterial-veno (V-A-V) ECMO. If cardiogenic shock is suspected secondary to myocarditis, expert consultation with an advanced heart failure team should be strongly considered.