Description and Proposed Management of the Acute COVID-19

Cardiovascular Syndrome

Running Title: Hendren et al.; Acute COVID-19 Cardiovascular Syndrome

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Abstract

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, systemic cytokine-mediated injury or stress-related cardiomyopathy. Although histologically unproven, SARS-CoV-2 has the potential to directly replicate within cardiomyocytes and 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 the evaluation 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. From these data, we propose a surveillance, diagnostic and management strategy that balances potential patient risks and healthcare staff exposure with improvement in meaningful clinical outcomes.

Key Words: coronavirus disease 2019; myocarditis; stress-induced cardiomyopathy

Non-standard Abbreviations and Acronyms

	· · · · · · · · · · · · · · · · · · ·
ACE2	angiotensin-converting enzyme 2
ACovCS	acute COVID-19 cardiovascular syndrome
CAR-T	chimeric antigen receptor T
COVID-19	coronavirus disease 2019
cMRI	cardiac magnetic resonance imaging
CRS	cytokine release syndrome
СТ	computed tomography
DIC	disseminated intravascular coagulopathy
cTnI	cardiac troponin I
ECMO	extracorporeal membrane oxygenation
EKG	electrocardiogram
GDMT	guideline-directed medical therapy
hs-cTnI	high-sensitivity cardiac troponin I
IL-6	interleukin 6
IVIG	intravenous immunoglobulin
LVEF	left ventricular systolic function
MERS	Middle Eastern respiratory syndrome
S	spike
SARS	severe acute respiratory syndrome

SARS-CoV-1	severe acute respiratory syndrome coronavirus-1
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
TMPRSS2	transmembrane serine protease 2



Introduction

Since the index cases were first reported in Wuhan, China in December 2019, Coronavirus Disease 2019 (COVID-19) due to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has become a global pandemic infecting >1 million individuals by early April, 2020^{1, 2}. In addition to systemic and respiratory complications, COVID-19 can manifest with an acute cardiovascular syndrome (what we have termed 'ACovCS', see Table 1 & Figure 1). In this document, we focus on a prominent myocarditis-like syndrome involving acute myocardial injury often associated with reduced left ventricular ejection fraction in the absence of obstructive coronary artery disease. This syndrome can be complicated by cardiac arrhythmias and/or clinical heart failure with or without associated hemodynamic instability including shock ^{1,3}. These cardiac complications can occur precipitously at any point during hospitalization and are increasingly being described as a late complication that can occur after improvements in a patient's respiratory status ^{4, 5}. ACovCS may be due to acute coronary syndrome, demand ischemia, microvascular ischemic injury, injury related to cytokine dysregulation or myocarditis ^{6,7}. The aim of this paper is to review the available data on ACovCS epidemiology, pathogenesis, diagnosis and treatment. From these data we propose a surveillance, diagnostic and management strategy that balances patient and health care provider risks with potential improvement in meaningful clinical outcomes.

Myocardial Injury in Patients with COVID-19

Acute myocardial damage during a viral illness may be inferred from rises in specific biomarkers, characteristic electrocardiogram (EKG) changes and/or new imaging features of impaired cardiac function. Prior experiences from Middle Eastern Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), COVID-19 and non-SARS

coronaviruses demonstrate that coronavirus can cause acute myocarditis ⁷⁻¹². In COVID-19, the frequency and differential patterns of troponin release in the context of a clinical presentation of a type 1 or 2 myocardial infarction, myocarditis or cytokine/stress related cardiomyopathy is not well defined. Anecdotal reports have described cases of acute myocardial injury characterized by marked cardiac troponin elevation accompanied by ST-segment elevation or depression on EKG, and angiography often without epicardial coronary artery disease or culprit lesions identified ^{11, 13}. These early data suggest that the dominant cause of myocardial injury for this phenotype is myocardial injury in the absence of epicardial coronary artery thrombosis. Additionally, myocarditis, systemic cytokine-mediated, stress-related cardiomyopathy, or microvascular thrombosis could produce an acute myocardial injury pattern (Figure 2).

Acute myocardial injury as assessed by troponin release alone appears to complicate a substantial minority of hospitalized patients with COVID-19, particularly patients that require intensive care. Analysis of a series of 52 critically ill patients in China with COVID-19 revealed myocardial injury (high-sensitivity cardiac troponin I [hs-cTnI] >28 ng/L) in 29% of patients ¹⁴. Analysis of a second Chinese single center retrospective report of 416 patients hospitalized with COVID-19 observed approximately 20% (82/416) of patients had an acute myocardial injury (cardiac troponin I [cTnI] >0.04 μ g/L) and patients with myocardial injury were older and had a higher burden of comorbid disease ¹⁵. Myocardial injury was associated with a higher observed mortality that persisted after adjustment for baseline characteristics and medical comorbidities ¹⁵. A report from a another Chinese multicenter retrospective study comprising data from 191 patients hospitalized with COVID-19 observed myocardial injury (cTnI >28 ng/L) in 1/95 (1%) of surviving patients compared with 32/54 (59%) of patients who did not survive ¹⁶. Lastly, results from a meta-analysis revealed abnormal cTnI values (>99th percentile) in 8-12% of

patients hospitalized in COVID-19 and elevations were associated with more severe complications and worse outcomes ¹⁷. The mean difference in cTnI value was 25.6 ng/L (95% CI 6.8–44.5 ng/L) between those with (n=123) and without (n=218) severe disease ¹⁷. Although the troponin samples were not systematically collected and their ascertainment may be influenced by indication bias, these data are supportive that acute myocardial injury is commonly observed in COVID-19 and is prognostic for worse outcomes.

The mechanism of acute myocardial injury in COVID-19 is unresolved. Several cases of clinically diagnosed myocarditis relating to COVID-19 (without histology or pathology, but with supporting imaging) have been reported, including one case requiring veno-arterial extracorporeal membrane oxygenation (ECMO)^{11, 18, 19}. The patient treated with ECMO was also treated with steroids, intravenous immunoglobulins and anti-viral therapy, and subsequently introrecovered ¹⁹. In a case series of 150 patients, 5/68 (7%) of reported deaths reported acute myocardial injury with heart failure and another 22/68 (32%) deaths reported acute myocardial injury with heart failure as contributing factor ²⁰. Limited autopsy and endomyocardial biopsy results have been reported, but a case report from Italy has described biopsy-proven acute lymphocytic myocarditis in an individual with COVID-19⁷. A second case report described a patient with COVID-19 presenting with acute myocardial injury and cardiogenic shock ¹². The patient underwent an endomyocardial biopsy which demonstrated low-grade myocardial inflammation and the absence of myocyte necrosis with localization of SARS-CoV-2 within macrophages, but not cardiomyocytes ¹². This case confirms that SARS-CoV-2 can reside within the heart, but does not provide evidence for cardiotropic viral cell entry. Altogether, these studies confirm that acute myocarditis is a mechanism of myocardial injury in some patients with

COVID-19, although the proportion of myocardial injury related to acute lymphocytic myocarditis remains uncertain.

Additional reports from Wuhan indicate a significant proportion of non-surviving patients also had elevated transaminases, lactate dehydrogenase, creatine kinase, d-dimer, serum ferritin, interleukin 6 (IL-6) and prothrombin time, which in totality suggest markedly elevated proinflammatory mediators and a cytokine profile similar to the cytokine release syndrome ^{15, 16}. This constellation of inflammatory cytokines has inherent similarities to chimeric antigen receptor T (CAR-T) induced cytokine release syndrome (CRS) which results in marked elevations of IL-6, and interferon- γ^{21} . For ACovCS, it is unclear to what extent such cytokine elevations cause or contribute to myocardial injury, left ventricular dysfunction and cardiac troponin elevation. Additional studies, including collection of endomyocardial tissue by biopsy and autopsy studies, will be required to delineate the pattern and proportion of ACovCS related to acute myocarditis versus general myocardial injury due to systemic cytokine dysregulation.

COVID Target Tissues

The majority of prior experience with myocardial injury associated with viral infections is gleaned from data deriving from infections not related to coronaviruses. For example, clinical syndromes with COVID-19 suggest a higher prevalence of myocardial injury compared with that observed with wild-type coxsackie virus infections. The outbreak of SARS-CoV-1 in 2003, the SARs pandemic, resulted in investigations that have the potential to inform our understanding of SARS-CoV-2. Investigation into SARS-CoV-1 revealed that the virus expresses numerous spike (S) proteins on the surface of the viral envelope that are vital to the transmission of infection (Figure 3)²². These S proteins bind via the S1 subunit to angiotensin-converting enzyme 2 (ACE2) expressed on host cells, but merely binding to ACE2 is not sufficient for cell infection

²². Viral cell entry requires the transmembrane serine protease 2 (TMPRSS2) expressed on host cells to perform critical protein priming that leads to conformational changes, viral cell entry and cell infection ^{22, 23}. Investigation into SARS-CoV-2 has confirmed the importance of the S1 protein binding to ACE2 on target cells and the expression of the TMPRSS2 protease for host cell infection ²⁴.

Mechanisms that disrupt the S1 subunit binding, ACE2 binding or TMPRSS2 protease activity pose potential therapeutic targets. This theory was tested with the evaluation of the effect of antibodies to the S protein obtained from the convalescent serum of SARS-CoV-2 patients. Antibody administration reduced viral cell entry in a concentration-dependent manner demonstrating partial successful inhibition of viral entry in an *in vitro* cell line ²⁴. Furthermore, the administration of anti-ACE2 antibodies has been demonstrated to inhibit SARS-CoV-1 and SARS-CoV-2 viral replication in an *in vitro* cell preparation in a dose dependent fashion further supporting the importance of the receptor as necessary for cellular entry ^{22, 24}. Additionally, results from early pre-clinical studies using recombinant ACE2 administration report effectively neutralizing SARS-CoV-1 and SARS-CoV-2 in vitro ²⁵. Lastly, inhibitors of the serine protease TMPRSS2 were effective in reducing cellular entry for both SARS-CoV-1 and SARS-CoV-2 in an *in vitro* model ²⁴. These studies clarify the mechanism of viral cell entry and highlight three distinct potential therapeutic targets that are theorized to reduce cellular entry and pathogenesis. The results from these small in vitro studies suggest anti-ACE2, TMPRSS2 inhibitors and inhibitors of S1 protein subunits may reduce viral propagation in host cells, although further study is required.

Given the essential nature of ACE2 for viral infection, the distribution of ACE2 expression is informative to elucidate the likely infected tissues and hypothetical mechanisms of

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injury. ACE2 is prominently found in type 1 and II lung alveolar epithelium, pericytes, cardiomyocytes, enterocytes in the small intestine including the duodenum, jejunum, and ileum, and arterial and venous endothelial cells ²⁶⁻²⁸. Autopsy studies in patients deceased due to SARS-CoV-1 have confirmed the presence of virus within cells that prominently express ACE2 including bronchiolar and alveolar epithelial cells, renal tubular epithelial cells, mucosal and crypt epithelial cells of the gastrointestinal tract, and cardiomyocytes ²⁹. Analyses of histologic samples of pulmonary tissue in patients with COVID-19 reveal a similar pattern of injury as was reported with SARS-CoV-1 ³⁰. Although these data are extremely limited for COVID-19 at this juncture, they offer proof of concept of direct cellular injury in tissues with ACE2 expression. The myocardial cellular targets for SARS-CoV-2 may include pericytes, cardiomyocytes, fibroblasts, and immune cells such as resident macrophages.

Myocardial Pathology

Pathological examination may help clarify whether myocardial injury predominately occurs indirectly due to systemic cytokines or directly due to viral cardiomyocyte infection or some other mechanism. Acute cellular injury due to SARS-COV-2 cardiomyocyte, pericyte or fibroblast infection via ACE2-mediated entry and subsequent viral replication is a theoretical but unproven process. Analyses of histologic specimens have demonstrated direct cellular viral infection of the myocardium and cells within the conduction pathways of the heart with SARS-CoV-1 ^{29, 31, 32}. Prior acute myocarditis experience with alternative viruses suggests direct cellular injury is related to a combination of cardiotropic viral entry into myocytes and the subsequent innate immune response that can lead to focal or diffuse myocardial necrosis ³³. Within a few days of this direct cellular injury, edema and necrosis can lead to contractile dysfunction and clinical symptoms ³³. If true in COVID-19, this delayed injury could potentially

manifest as an abrupt clinical decline after several days of stability. Cardiotropic viruses, such as SARS-CoV-1, are typically cleared from the myocardium within 5 days; however, infrequently the virus may persist in the myocardium for several weeks to months ³⁴. Presuming SARS-CoV-2 can directly infect the myocardium, any associated myocarditis will predominately be manifest in the acute or subacute stage. It is also uncertain if SARS-CoV-1 or SARS-CoV-2 leads to the production of cardiac auto-antibodies that develop due to molecular mimicry, as previously demonstrated between Coxsackie B virus proteins and the S2 regions of cardiac myosin ³⁵. Whether viral persistence or inflammation from COVID-19 can cause a chronic dilated cardiomyopathy as occurs after coxsackie B virus myocarditis is also unknown.

Alternatively, myocardial injury in COVID-19 may also result from profound inflammatory activation and cytokine release ¹⁶. Analysis of a small case series of minimally invasive autopsy in three patients deceased from COVID-19 described the presence SARS-CoV-2 within alveolar tissue ³⁶. SARS-CoV-2 was not isolated from cardiac tissue, but degenerative changes and necrosis suggested a secondary mechanism of injury ³⁶. These preliminary observations raise the possibility that SARS-CoV-2, unlike SARS-CoV-1 as described above, may not directly cause cellular injury. Indeed, acute myocardial injury in the setting of non-COVID-19 viral immune activation can result from immune-mediated injury due to activated T and B cells leading to an inflammatory cascade, cytokine production and antibody production ³³. ³⁷. Further studies in stress-induced and non-COVID-19 viral associated cardiomyopathy have associated increased levels of cytokines with myocardial injury ^{38, 39}. As discussed, a profound inflammatory response with marked cytokine production commonly occurs in hospitalized patients with severe or critical COVID-19 ¹⁶. This marked inflammatory response can also lead to the development of disseminated intravascular coagulopathy (DIC) in critically ill patients. In

183 consecutive Chinese patients admitted with COVID-19, coagulopathy was associated with higher mortality and 15/21 (71%) of non-surviving patients met criteria for DIC ⁴⁰. Localized pulmonary arteriolar thrombosis was described in SARS and pulmonary emboli have been reported in COVID-19 ⁴¹. As such, microvascular thrombosis in coronary vessels due to DIC is another potential but unproven mechanism that may contribute to myocardial injury ⁴².

In short, SARS-CoV-2 has the potential to infect cardiomyocytes, pericytes and fibroblasts via the ACE2 pathway leading to direct myocardial injury, but that pathophysiological sequence remains unproven. A second hypothesis to explain COVID-19 related myocardial injury centers on cytokine excess and/or antibody mediated mechanisms. Further investigation via autopsy and endomyocardial biopsy tissue will be needed to clarify which of these is the predominate mechanism of injury in ACovCS.

Historical Outcomes

Patients with acute viral myocarditis commonly present following a viral syndrome with clinical heart failure, chest pain, abnormal electrocardiograms that can mimic an acute coronary syndrome, and/or ventricular arrhythmias ^{43, 44}. This constellation of findings is increasingly being described in patients infected with COVID-19, raising suspicion for acute viral associated injury from a myocarditis-like presentation ⁶. There is a paucity of published data on the cardiac complications of MERS and SARS. Patients with pre-existing cardiovascular disease have increased mortality observed for both SARS and COVID-19; however, cardiac complications appear to be less prevalent in SARS compared with COVID-19 ^{16, 45}.

Diagnosis

Historically, patients are typically diagnosed with acute myocarditis if they have <30 days of symptoms with an abnormal troponin and cardiac magnetic resonance imaging (cMRI) findings

meeting the revised Lake Louise 2018 criteria ^{46, 47}. In non-COVID-19 cases, endomyocardial biopsy has been traditionally recommended in fulminant presentations to exclude the rare presentation of eosinophilic, hypersensitive, and giant-cell myocarditis ⁴⁸. However, in the setting of COVID-19, such an approach may not be feasible due to instability of the patient, procedural risk and risk of healthcare staff exposure, especially if the biopsy results would not change clinical management. Patterns of delayed myocardial enhancement consistent with acute myocarditis have also been described in contrast-enhanced EKG-gated multidetector computed tomography (CT) in non-COVID-19 cases ^{49, 50}. This may be a useful rapid and noninvasive diagnostic test to assess for myocardial injury in COVID-19 patients who complete a CT-scan for non-cardiac reasons and represents an opportunity for investigation.

Given the extremely contagious and morbid nature of COVID-19, the priorities related to managing and diagnostic options for a patient with ACovCS include reducing staff/patient exposures, a goal that can be facilitated by limiting testing and patient transfer for diagnostic procedures, especially those that do not directly influence patient management. Another consideration is to limit testing that requires terminal room cleaning required by patient transfer, as that process can add significant delays to diagnostic testing for other patients. Such strategies may result in increased uncertainty about the diagnosis, but are unlikely to increase adverse short-term outcomes in patients without fulminant presentations. For example, for patients noted to have acutely elevated troponin, if a type 1 myocardial infarction can be excluded on clinical grounds, then a biopsy is unlikely to change immediate clinical management whether the clinical syndrome is due to myocarditis, cytokine-induced myocardial injury, or a type 2 myocardial infarction. As such, routine endomyocardial biopsy in patients with active COVID-19 with abnormal cardiac biomarkers, regardless of fulminant or non-fulminant presentation, is

discouraged. This strategy is aligned with recent American College of Cardiology recommendations ⁵¹. However, an exception to that approach could be a COVID-19 patient with hemodynamic and/or electrophysiologic instability who undergo coronary angiography to exclude obstructive coronary artery disease. In that setting, the patient is already in the catheterization laboratory so the incremental infectious risk is reduced since additional transport is not needed; such opportunities may be useful to gain insights into the mechanism of the acute myocardial injury, including the possibility of giant cell myocarditis which presumably can still occur during the COVID-19 pandemic.

In accordance with these guiding principles, the majority of patients with an abnormal troponin in the setting of COVID-19 infection can be followed with expectant management until recovery from the acute viral syndrome. Extrapolating from prior experiences, patients with COVID-19 and myocardial injury whom are hemodynamically and electrophysiologically stable with mild-moderate elevations of troponin should not routinely undergo an echocardiogram, angiography or cardiac imaging. These diagnostic studies likely can be avoided altogether, or delayed until recovery from COVID-19 unless the patient clinically deteriorates and develops hemodynamic instability, shock, ventricular arrhythmias or a severely elevated or rapidly rising troponin (Figure 4). However, if the treating clinician has the ability to perform point-of-care cardiac ultrasonography without increasing COVID-19 exposure, this would be reasonable to perform, as a low ejection fraction would identify higher-risk patients and support earlier initiation of guideline directed medical therapy once the patient is stable. However, unnecessary or repeated imaging not vital to clinical decision-making should be avoided in accordance with the American Society of Echocardiography COVID-19 statement ⁵². Patients discovered to have newly diagnosed depressed left ventricular systolic function (LVEF) without troponin elevated

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are more likely to have pre-existing cardiomyopathy than myocarditis. While the lack of definitive diagnostic studies may temporarily increase diagnostic uncertainty, it reduces the risk of COVID-19 transmission to staff and in clinically stable patients seems less likely to compromise short term (<60 day) patient outcomes.

Historical Treatments for SARS

Similar to COVID-19, SARS presented with a spectrum of symptoms and the majority of patients only required supportive care ⁵³. Several antiviral agents were used empirically in patients with severe respiratory compromise including ribavirin ⁵³. Ribavirin for SARS was eventually abandoned due to a lack of antiviral activity against SARS-CoV-1 and lack of efficacy in clinical trials ^{54, 55}.

Like COVID-19, patients with SARS developed progressive respiratory failure despitedeclining viral loads and rising antibody concentrations, a deterioration theorized to be an immune-mediated injury related either antibodies or elevated cytokine levels ^{53, 56, 57}. Steroid protocols were developed ranging from intravenous hydrocortisone 2 mg/kg four times daily to intravenous methylprednisolone 500 mg daily for five days with various taper protocols ⁵³. Steroid treatment for SARS yielded inconsistent benefit with some studies associating steroids with increased mortality and higher rate of intensive care, while others suggested modest radiographic or oxygen improvements ⁵³. A postmortem series of patients detected high viral loads in patients up to 30 days after illness onset, possibly because corticosteroids prolonged the duration of viral replication ⁵⁸. Additional therapies including tumor necrosis factor alphablockers, and convalescent plasma with anti-SARS-CoV-1 antibodies were proposed, but not rigorously studied. Although a concern, acute myocardial injury including myocarditis appeared

uncommon and there was scant published guidance for the management of SARS-CoV-1 myocardial injury.

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 ⁵⁹. 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 ⁵⁹. The study authors concluded that hydroxychloroquine had a significant effect and led to rapid SARS-CoV-2 clearance ⁵⁹. 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 ⁶⁰.

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 ⁵⁷. 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 ⁶¹. Additional *in vitro* testing of a human cell line demonstrated markedly reduced SARS-CoV-2 activity ⁶². 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 ⁶². Both hydroxychloroquine and antiviral therapies may increase the risk for torsades de pointes via QTc prolongation ⁶³. 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 ⁶⁴. 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 ⁶⁵. 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 ¹⁶. 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 ⁵⁸.

As discussed above, cytokine 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 ⁶⁶. 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 ^{21, 67}. 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 ⁶⁸⁻⁷⁰. In the interim, these agents can be considered for compassionate use on a case-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 ⁷¹. 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 ⁷². 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 ⁷³. 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 troponin⁷⁴. This recommendation is based on experimental animal models and several retrospective observational studies ⁷⁴⁻⁷⁶. 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 ⁷⁷. 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

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described successful rescue of patients with cardiogenic shock with use of veno-arterial (VA), and veno-arterial-veno (V-A-V) ECMO ^{5, 12, 19}. If cardiogenic shock is suspected secondary to myocarditis, expert consultation with an advanced heart failure team should be strongly considered.

Summary

In conclusion, COVID-19 is associated with the development of an associated cardiovascular syndrome including acute myocardial injury, arrhythmias, and cardiomyopathy that we have termed Acute COVID-19 Cardiovascular Syndrome (ACovCS). It is uncertain to what extent the acute systolic heart failure is mediated by myocarditis, cytokine storm, microvascular dysfunction, small vessel thrombotic complications, or a variant of stress-induced cardiomyopathy. Patients with elevated troponin who are otherwise clinically stable do not require extensive cardiac imaging during the acute phase of COVID-19 if point of care cardiac ultrasound is not available. Patients with hemodynamic instability or ventricular arrhythmias require more detailed evaluation, cardiology consultation and consideration for enrollment in clinical trials or experimental therapies.

Acknowledgements: None

Sources of Funding: None

Disclosures: NH, MD and LC report no relevant conflicts of interest or disclosures. BB has received consulting fees from Bristol Myers Squibb, scPharmaceuticals, Baxter Healthcare Corporation , Sanofi-Aventis, Relypsa; and serves on the Clinical Event Committee for GUIDE

HF Trial sponsored by Abbott Vascular, and Data Safety Monitoring Committee of ANTHEM trial (Autonomic REGULATION Therapy to Enhance Myocardial Function and Reduce progression of Heart Failure with reduced ejection fraction) sponsored by Liva Nova.



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Spectrum of Acute COVID-19 Cardiovascular Syndrome (ACovCS)	
Acute Coronary Syndrome (STEMI or NSTEMI)*	Chest Pain, Elevated Troponin, Wall Motion Abnormalities and/or ST-depression or Elevation \pm T-wave abnormalities.
Acute Myocardial Injury without Obstructive CAD†	Troponin Elevated ± Additional Symptoms.
Arrhythmias	Atrial Arrhythmias, Ventricular Tachycardia, Ventricular Fibrillation, and/or Complete Heart Block**.
	De novo Systolic Dysfunction
Heart Failure ± Cardiogenic Shock	Myocarditis or Myopericarditis
	Cytokine mediated Cardiomyopathy
	Stress-induced Cardiomyopathy
	Mediated via other risk factors (e.g., atrial arrhythmias)
	Acute on Chronic Decompensated Systolic Dysfunction
	± Elevated troponin
	Recurrent Systolic Dysfunction after LVEF Recovery
	Heart Failure with Preserved LVEF (HFpEF) ‡
Pericardial Effusion	± Tamponade
Thromboembolic Complications	Arterial Thromboembolism, Deep Vein Thrombosis, Intracardiac Thrombus, Microvascular Thrombi**, Pulmonary Embolism, Stroke

 Table 1. Spectrum of Acute COVID-19 Cardiovascular Syndrome (ACovCS)

* Reported with obstructive, non-obstructive, or no coronary artery disease. † It is uncertain if an abnormal troponin is required prior to onset of ACovCS. Additionally, patients are reported to have either non-obstructive or no epicardial coronary artery disease. ‡ Unknown at this time whether Heart Failure with Preserved LVEF is part of this spectrum. ** Although these complications may be anticipated with our incomplete understanding of COVID-19, to our knowledge reports of heart block or cardiac microvascular thrombi have not been published to date.

Abbreviations: CAD, coronary artery disease; LVEF, left ventricular systolic dysfunction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Figure Legends

Figure 1. Spectrum of the Acute COVID-19 Cardiovascular Syndrome

The spectrum of the Acute COVID-19 Cardiovascular Syndrome (ACovCS) encompasses a variety of cardiovascular syndromes described for patients presenting with COVID-19. Reports of pericardial effusions and cardiac tamponade in patients with COVID-19 have been published. Although the prevalence of pericardial effusion in ACovCS remains uncertain, significant effusions do not appear to be common. Clinical images are representative of the proposed ACovCS disease spectrum and several, but not all images are from patients with ACovCS. ^a Reported with obstructive, non-obstructive, or no coronary artery disease.

^b It is uncertain if an abnormal troponin is required prior to onset of ACovCS and patients are reported to have either non-obstructive or no epicardial coronary artery disease.

^c Significant uncertainty remains regarding the etiology and prevalence of the acute myocardial injury for patients without obstructive CAD and COVID-19. While myocarditis, cytokine storm, or stress cardiomyopathy are leading considerations, additional potential etiologies include hypoxemia and microvascular dysfunction from small vessel thrombosis. Abbreviations: ACovCS, Acute COVID-19 Cardiovascular Syndrome; CAD, coronary artery disease; COVID-19, Coronavirus Disease 2019; NSTEMI, non-ST-elevation myocardial

infarction; STEMI, ST-elevation myocardial infarction.

Figure 2. Potential Mechanisms of Myocardial Injury in Acute COVID-19 Cardiovascular Syndrome

Multiple mechanisms have the potential to result in non-ischemic myocardial injury in COVID-19. ^a Myocardial injury defined as cardiac troponin value >99th percentile of the upper reference limit. Abbreviations: CV, cardiovascular; COVID-19, Coronavirus Disease 2019.

Figure 3. SARS-CoV-2 Host Cell Entry

A - Simplified mechanism of SARS-CoV-2 viral entry to host cells. The SARS-CoV-2 virus expresses spike proteins with an S1 subunit that binds to ACE2 expressed on host cells. B – After binding to host ACE2, the host serine protease TMPRSS2 performs critical protein priming which leads to conformational changes, viral cell entry and cell infection. C – Antibodies to the S1 subunit of the spike protein, ACE2 and TMPRSS2 are potential therapeutic targets which reduce viral infectivity. Abbreviations: ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; Transmembrane serine protease 2, TMPRSS2.

Figure 4. Proposed Assessment and Management of ACovCS with Acute Myocardial Injury

Proposed Assessment and Management of ACovCS with Acute Myocardial Injury

^a If the treating clinician has the ability to provide a point of care cardiac ultrasonography without increasing COVID-19 exposure or personal protective gear use, limited LVEF assessment can be considered as a depressed systolic function would identify higher-risk patients.

^b Repeat troponin testing is indicated with a deterioration of clinical status.

^c This pathway attempts to balance the imperfect trade-offs of increased diagnostic uncertainty without compromising patient outcomes while minimizing unnecessary staff exposures and testing that will not immediately change clinical care.

^d The 2015 Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities task recommends abstinence from competitive sports or aerobic activity for a period of 3-6 months until resolution of myocardial inflammation.

^e Assessment of the left ventricular ejection fraction should be considered at early follow-up for patients with an abnormal troponin during hospitalization to either identify patients with reduced systolic function or to complete a full cardiac assessment. Complete assessment should occur once a patient is no longer considered infectious in accordance with Center for Disease Control recommendations for the discontinuation of transmission-based precautions for patients with COVID-19.

^{**f**} There are currently no evidence-based therapies for COVID-19 with robust clinical evidence of efficacy. Enrollment into a clinical trial should be strongly considered if available at the treating center. Additional treatment with anti-viral, anti-cytokine and additional investigational drugs should be completed on a case-by-case basis after consultation with a multidisciplinary team.

^gConsideration of pulmonary arterial catheters, inotropic and/or mechanical support (i.e. intraaortic balloon pump, temporary left ventricular support device, VA-ECMO) should be completed on a case-by-case basis taking into account patient characteristics, availability of appropriately trained staff and the ability of the healthcare institution to safely manage a support device.

^h Evidence of acute myocarditis by imaging or biopsy within myocardial tissue may modify the choice and dosing regimen of therapies.

Abbreviations: ACovCS, Acute COVID-19 Cardiovascular Syndrome; COVID-19; Coronavirus Disease 2019; CT, computed tomography; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PA, pulmonary artery; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia.









