# Coronavirus Disease 2019 (COVID-19) Pandemic Implications in Pediatric and Adult Congenital Heart Disease

**Running title:** *Alsaied et al.; COVID-19 in Pediatric and Congenital Heart Disease*

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## ABSTRACT

The corona virus disease -2019 (COVID-19) is a recently described infectious disease caused by the severe acute respiratory syndrome corona virus 2 with significant cardiovascular implications. Given the increased risk for severe COVID-19 observed in adults with underlying cardiac involvement, there is concern that patients with pediatric and congenital heart disease (CHD) may likewise be at increased risk for severe infection. The cardiac manifestations of COVID-19 include myocarditis, arrhythmia and myocardial infarction. Importantly, the pandemic has stretched health care systems and many care team members are at risk for contracting and possibly transmitting the disease which may further impact the care of patients with cardiovascular disease. In this review, we describe the effects of COVID-19 in the pediatric and young adult population and review the cardiovascular involvement in COVID-19 focusing on implications for patients with congenital heart disease in particular.

**ABBREVIATIONS**

ACE-I Angiotensin-converting enzyme inhibitor

ACE Angiotensin Converting Enzyme

ACHD Adult congenital heart disease

AP Anatomical and Physiological

ARB Angiotensin Receptor Blocker

CDC Centers of Disease Control and Preventions

CHD Congenital Heart Disease

COVID-19 Corona virus Disease of 2019

NSAIDs Non-Steroidal Anti Inflammatory Drugs

SARS-CoV2 Severe Acute Respiratory Syndrome Corona virus 2

WHO World Health Organization

Corona viruses are important pathogens that can infect humans and animals. At the end of 2019, a novel corona virus was isolated in Wuhan, a city in China, as a cause of a cluster of severe cases of pneumonia and acute respiratory distress syndrome [1]. The virus rapidly spread around China and the world. On March 11th 2020, COVID-19 was declared as a pandemic by the WHO and the virus has infected hundreds of thousands of patients and thousands of health care providers [2, 3]. While children in general seem to have milder or even asymptomatic forms of the illness, there is little to no data in children with chronic medical conditions, specifically heart and lung disease [4, 5]. The knowledge and experience in caring for patients with COVID-19 is rapidly evolving and thus it is crucial for all health care providers to be aware of the potential impact of COVID-19 on patients with congenital heart disease (CHD).

COVID-19 is particularly important for cardiac team members for the following reasons:

1- COVID-19 has higher morbidity and mortality in adult patients with acquired cardiac disease.
2- COVID-19 may affect and impact the cardiovascular system.
3- COVID-19 may cause symptoms that mimic symptoms of cardiovascular disease like cyanosis and shortness of breath commonly seen in forms of worsening cardiac disease.
4- Cardiac care team members are at risk for acquiring COVID-19 and may play a role in spreading the disease between patients and in the society at large.
5- Patients with CHD are known to have higher risk for complications with viral illnesses [6, 7].
6- COVID-19 may stretch our health care system and our resources which may impact the care of patients with cardiovascular disease.

Based on the COVID-19 pandemic trends it is expected that many of the cardiovascular care team members will be exposed to patients with COVID-19 in the coming weeks and months. In anticipation of the spread of COVID-19 many hospitals and cardiology practices have

changed their care models and policies to accommodate the care of patients impacted by COVID-19 and prevent the spread of the disease.

The objective of this review is to explore the current knowledge about COVID-19 potential effects on the cardiovascular system in the pediatric cardiology and adult CHD population. In addition, we will review the prevention practices and the impact on the health care team wellness.

## Methods

Due to the emergent and evolving nature of COVID-19 we reviewed the published literature in MEDLINE through PubMed and critically assessed early reports using a search for COVID-19 and SARS-CoV-2 in medRxiv and bioRxiv from January 1st 2020 until March 23rd 2020. We had personal communications with multiple organizations around the world caring for children and adults with CHD and we reviewed social media reports from leaders in the field of congenital cardiology. In addition, the websites of the health organizations including WHO and CDC were reviewed to provide up to date numbers and infection control recommendations. A congenital cardiology email list serve was initiated on the 15th March to facilitate discussion and share experiences and ideas on topics such as: strategies to manage outpatient clinic, inpatient service, procedure prioritization, screening, telemedicine and dealing with staff illness and school closures and we share some thoughts and information from physicians on the frontline of care of patients with COVID-19.

## Pathophysiology

SARS-CoV2 belongs to the Coronaviridae family. As a group this family has a single strand RNA genome [8]. The viral RNA closely resembles the RNA of two bat corona viruses (88% identical) [9]. The hypothesis is that the bat is likely the primary source of the virus although the

mechanism of transfer from bat to human is still unclear (i.e. whether it was through direct transmission or whether there was an intermediate host) [8, 9]. The virus is also closely related (79% identical) to the SARS corona virus which was responsible for an outbreak in China in 2002-2003 and 50% identical to the Middle East Respiratory Syndrome corona virus that caused an outbreak in the Arabian Peninsula in 2012 [8-10]. Importantly the virus enters the cells using the angiotensin converting enzyme 2 (ACE-2) [11, 12]. SARS-CoV2 spike protein binds to the ACE-2 and the virus enters the cells through endocytosis [13, 14]. ACE-2 are expressed on the surface of epithelial cells within the alveoli and small intestine which explain the respiratory and gastrointestinal symptoms associated with the disease [14, 15]. ACE2 is a membrane bound protein that is also expressed in vascular endothelium, renal tissue and cardiovascular tissue [16]. ACE converts angiotensin I to angiotensin 2 while ACE-2 deactivates angiotensin 2 [17]. Angiotensin 2 stimulates lung injury and ACE-2 serves a role in lung protection as it deactivates angiotensin 2. Viral binding to ACE-2 deactivates the protective role of ACE-2 and that may contribute to severe lung injury seen with COVID-19 [13, 15].

**Epidemiology**

More than 2.5 million cases of COVID-19 have been confirmed worldwide with more than 175,000 deaths attributed to COVID-19 according to the WHO website as of 04/23/2020 [2, 18]. Of these cases 84,000 cases were reported from China where the disease peaked between mid-January and early February [2, 19, 20]. The initial patients had worked or visited a seafood "wet" market in Wuhan that sold live animals and was closed subsequently for infection control [21, 22]. Human to human spread subsequently became the main source of transmission [2, 19]. The disease then spread around the world initially through patients travelling from China followed by local transmission [5]. As of April 23rd 2020, there were 800,926 confirmed cases in the United States and over 40,000 deaths due to COVID-19 according to the Centers for Disease

Control and Prevention (CDC) website [5]. Transmission is thought to occur mainly via respiratory droplets produced during talking, coughing or sneezing similar to other corona viruses and similar to the influenza virus [23]. Transmission from asymptomatic individuals or patients in the incubation period has been documented [24, 25]. The virus can also stay viable in aerosols up to 2.6 hours and can stay for hours to days on surfaces, especially plastic and stainless steel [23].

**Clinical presentation**

In adult patients the incubation period is up to two weeks with a median of 4-5 days [25-27]. More than 80% of infected individuals will remain asymptomatic or develop mild pneumonia [11]. About 15% of patients will develop severe pneumonia and another 5% of patients will develop critical disease with respiratory and multi-organ failure and shock [11]. Fever is the most common symptom reported in most adult patients followed by fatigue and dry cough [1, 28]. Other symptoms include myalgia, anorexia, dyspnea, loss of sense of taste and smell (anosmia) and less commonly rhinorrhea, headache and sore throat [28-30]. Gastrointestinal symptoms including diarrhea and nausea have also been reported in up to 51% of patients [31, 32]. The median time to hospital admission is 7 days from the start of symptoms [31]. According to the WHO, recovery happens in two weeks in mild cases and in up to 6 weeks in severe cases [3, 33]. The median time from symptoms to death in severe cases is estimated to be between 13-17 days [34]. Estimating case fatality rate is challenging and is evolving depending on the testing policies in each country and the age and risk profile of the infected patients. The rates reported range from 0.4 % up to 5.8 % [11, 35-37].

**COVID-19 in Children and Young Patients**

While the severity and mortality due to COVID-19 is higher in older patients, the virus can also infect children and young adults [38, 39]. Overall only 2% of the reported cases from China were in individuals younger than 20 years and less than 1% were younger than 10 years [11, 40]. Fortunately, the disease in children is reported to be milder than adults although severe cases with multi-organ involvement have been reported [41, 42]. A nationwide case series from China included 2143 pediatric patients with COVID-19 [43]. Of those, 731 had positive testing while the rest had highly suspicious clinical picture [43]. Severe disease with hypoxia was reported in 5% of the cases while a total of 13 patients had critical disease with acute respiratory distress syndrome or multi-organ failure and one death was reported in a 14 year-old [43]. Compared to older children, infants had a high risk for severe disease [43]. Another study looked at all the cases tested and treated at the Wuhan Children's Hospital which is the only hospital to test and treat Children in Wuhan for COVID-19 [11]. Of 1391 patients tested, 171 (12.3%) were confirmed to have SARS-COV2 infection at a median age of 6.7 years. Of these 16% were asymptomatic and only 42% were febrile at some point during the illness. During the course of the admission only 3 of 171 patients required intensive care unit and mechanical ventilation and all 3 had preexisting conditions (intussusception, leukemia on maintenance chemotherapy and hydronephrosis). One 10 month old patient died but the patient also had intussusception with multi-organ failure [11].

**COVID-19 and the cardiovascular system**

The data on cardiovascular involvement with COVID-19 is evolving [44]. COVID-19 may result in cardiac injury through multiple potential mechanisms, including:

1. Cardiomyocyte injury due to an acute and severe inflammatory response as seen during a cytokine storm

2. Viral invasion of cardiomyocytes resulting in cellular damage
3. Ischemic injury in the presence of severe hypoxia as a result of acute lung injury

A recent meta-analysis evaluated the prevalence and effect of preexisting cardiovascular disease in patients with COVID-19 [45]. The study evaluated 1527 patients and reported the prevalence of hypertension, cardiac and cerebrovascular disease, and diabetes to be 17%, 16% and 10% respectively [46]. Studies from China and Italy consistently show that preexisting cardiovascular disease increase the risk of mortality in patients with COVID-19 [11, 47]. The mechanism for increased risk of mortality is likely multifactorial including older age in patients with cardiac morbidities and altered immunologic response due to age and diabetes [48, 49]. A population with potentially increased risk is patients with heart transplantation due to immunosuppression and two case reports describe COVID-19 in heart transplant patients [50-52]. One patient had mild disease while the other had severe disease. Both patients were successfully treated with steroids, intravenous immunoglobulins and antibiotics and both survived without rejection [50, 51].

Multiple cardiovascular sequelae are reported in patients with COVID-19 which may lead to or exacerbate cardiac disease [44]. Myocardial injury evidenced by elevated troponin is common in COVID-19 especially in patients with severe disease [44, 53]. Arrhythmia is also commonly seen in COVID-19 patients and while nonspecific, palpitations are one of the presenting symptoms in 7% of the patients [31, 44, 54]. Arrhythmia was noted in 16% of a group of hospitalized adult patients in China and was more common in the ICU setting [31]. There remains uncertainty about the specifics of the type of arrhythmia and there are no data in children. Arrhythmia could be related to stress, inflammation and metabolic abnormalities but the development of new malignant arrhythmias should raise the suspicion for an underlying myocarditis [44, 54]. Myocarditis is a significant contributor to mortality in up to one third of cases with severe COVID-19 and was the primary cause of death in 7% of the patients [55]. Autopsy found evidence

of fulminant myocarditis with inflammatory mononuclear infiltrates in the myocardial tissue in some cases although the prevalence and risk factors for myocarditis are yet to be described [44]. Heart failure was reported in up to 23% of patients with COVID-19 with a high prevalence of mortality [56]. Whether this is due to unmasking of pre-existing left ventricular dysfunction or new onset of cardiomyopathy due to myocarditis remains unclear [56]. Finally some severe cases may progress to cardiogenic shock and extracorporeal membranous oxygenation support may be considered in these cases although the prognosis is poor with 83% mortality in one report [44, 57].

**Special Considerations in the Pediatric Cardiology and Adult Congenital Heart Disease Population**

CHD affects up to 1% of the general population and remains the leading cause of infant mortality due to congenital malformations [58]. The survival has improved significantly and it is estimated that there are 2.4 million patients with CHD living in the United States of whom 1.4 million are adults with CHD [59]. Fortunately, children have low mortality due to COVID-19 with only few reported deaths [40, 42, 60]. Nevertheless, it is unclear what the risk of severe COVID-19 is in a patient with CHD who becomes infected. Given the experience in patients with CHD with previous viral diseases including influenza and respiratory syncytial virus, it is reasonable to expect that those with severe CHD are at higher risk of having severe COVID-19 [6, 7]. The AHA/ACC guidelines for the care of adults with CHD utilize an anatomical and physiological (AP) classification for the severity of CHD. This can be useful while assessing the risk for COVID-19 in this population as patients with more severe disease (AP Class IB-D, IIA-D and IIIA-D) are likely at higher risk for COVID-19 disease [61, 62]. These AP Classes are summarized in **Table 1**. On March 18th 2020, the British Congenital Cardiac Association issued a statement to identify vulnerable patients with CHD [63]. These highest risk groups are

summarized in **Table 2**. In addition to the cardiac morbidity, many patients with CHD also have other organ involvement including chronic lung disease, cirrhosis and renal disease which may also increase the risk of COVID-19 [64]. We want to emphasize that there is very limited evidence to make firm recommendations and that these are based on the experience with previous viral diseases [6, 7]. Of note cardiovascular morbidities like diabetes and hypertension may also increase the risk of COVID-19 in pediatric patients similar to that seen in adult patients. Additionally, diabetes, hypertension, and acquired cardiovascular disease may co-exist in adults with CHD, potentially further increasing their risks. It is also important to note that many symptoms of COVID-19 may mimic symptoms of worsening cardiac conditions in the CHD population. Symptoms such as shortness of breath, palpitations and fever are commonly seen in endocarditis which is a major concern in patients with CHD [65]. The same symptoms can also be seen in heart failure decompensation due to a viral illnesses and these considerations should be kept in mind during the COVID-19 pandemic.

## COVID-19 and Medications

### Aspirin

Aspirin is commonly used in the pediatric and adult population with CHD for its antiplatelet effects at a low dose of 3-5 mg/kg/day [66]**.** There is an association between the use of aspirin and the development of Reye syndrome, a rare form of hepatic encephalopathy, in young children taking high dose aspirin for Kawasaki disease who have concurrent infection with influenza or varicella [67, 68]. There are no reports of Reye syndrome in patients on low dose aspirin typically used with CHD or with COVID-19 [60]. Due to that we currently do not stop aspirin in children or adults with CHD and COVID-19.

**Ibuprofen and Nonsteroidal anti-inflammatory medications (NSAIDs)**

There is no convincing evidence that NSAIDs are harmful in COVID-19 although some clinicians suggested a possible negative impact if used early in the course of the disease for fever [69]. The WHO and the European Medicines Agency currently approve the use of ibuprofen and NSAIDs in COVID-19 [70, 71]. The British Congenital Cardiac Association suggested avoiding NSAIDs to treat fever in COVID-19 [63].

**Angiotensin converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARB)**

The ACE-2 is used by the virus for cell entry [44]. At this point there is insufficient data to suggest that ACE-i/ARB could affect the course of COVID-19 [11, 44]. ACE-i/ARBs suppress Angiotensin II or blocks its effect on its receptor. This is a positive effect to blunt the pulmonary inflammatory response and may result in upregulation of ACE-2 which can be a positive effect for the same reason but at the same time carries the potential risk of increasing SARS-CoV-2 entrance to the alveolar cells [56]. In the Chinese data the rate of hypertension was significantly higher in patients who died post COVID-19. Whether this is because of the older age and multiple comorbidities in the patients with hypertension or if it has any relationship to the ACE-i/ARBs use is unclear [56, 72]. It is our practice currently not to stop ACE-i/ARB in patients who have COVID-19 as stopping these medications could have harmful effects. The ACC, American Heart Association and the Heart Failure Society of America issued a statement recommending not adding or removing these medications for patients who are taking these medications if diagnosed with COVID-19 and to follow an individualized approach [73].

**Anticoagulation**

Coagulation cascade abnormalities and disseminated intravascular coagulation (DIC) are reported in patients hospitalized with severe COVID-19 disease [44, 56, 74]. We suggest continuing anticoagulation in mild cases with monitoring from the prescribing physician. Adjusting anticoagulation can be done as needed in cases of severe COVID-19.

**Beta blockers, diuretics and antiarrhythmic medications**

There is no data to suggest any interaction of COVID-19 with these medications and we suggest continuing these medications and adjusting as needed by the prescribing physician.

**Medications used to treat COVID-19 effects on the cardiovascular system (Table 3)**

The interaction between COVID-19 treatments and the cardiovascular system are previously reviewed in JACC [44]. Several medications are under active investigation to treat COVID-19 [75]. Antiviral medications being trialed include ritonavir/lopinavir which can cause QT prolongation [44]. Ribavirin, another antiviral being investigated, and ritonavir/lopinavir can also interact with anticoagulants [44, 76]. Remdesivir, an investigational antiviral medication used to treat Ebola virus, is being trialed and although cardiovascular toxicities have not been reported, among 175 patients one developed hypotension and cardiac arrest after the loading dose [44, 77]. Chloroquine and hydroxychloroquine, antimalarial agents, have been shown *in vitro* to have inhibitory activity on SARS-CoV2 due to increasing cellular endosomal PH and thus preventing the viral endocytosis into the cells [75, 78-80]. This medication has been trialed *in vitro* and has been shown to be effective. However, there is limited human data to support effectiveness in humans [80, 81]. One small study treated 20 patients who were asymptomatic or had mild COVID-19 with hydroxychloroquine in combination with azithromycin and showed a significant decrease in viral load in treated patients [81]. The results should be taken with

caution as the medication was previously tried in cases of influenza, HIV and zika virus and showed effectiveness *in vitro* without any positive effect in humans [80]. Of note these agents have QT prolonging effects which should be taken into consideration especially when combined with hypokalemia, hypomagnesemia, myocarditis or other QT prolonging medications. This includes azithromycin, another commonly used antibiotic in respiratory infections with QT prolonging effects that is being trialed in COVID-19 infections [44, 75]. This would be of particular concern in patients in an intensive care unit setting where a variety of QT affecting medications and physiologic conditions might put patients at risk of myocardial hypersensitivity and arrhythmia risk. A list of these medications can be found at https://www.crediblemeds.org/.

## Considerations for the Cardiac Care Team

### Prevention

Screening all patients entering a health care facility for COVID-19 symptoms including fever and respiratory symptoms, travel and exposure to COVID-19 cases is essential for early identification of potential COVID-19 patients and to allow care team members to wear appropriate personal protective equipment (PPE) (**Figure 1**) [82]. Screening may be through the phone before the patient arrives and should employ the use of interpretation services when needed. Non-urgent cardiac visits should be rescheduled for a later date, particularly if the patient has viral symptoms without concern for possible worsening cardiovascular disease. Urgent cardiac visits with symptomatic patients (or if asymptomatic but with a high-risk exposure) should include the use of a facemask by the patient and ideally a separate waiting rooms [82]. Any caregiver entering the room for a confirmed or suspected COVID-19 case should wear a gown, gloves, eye protection and a respirator (e.g. N95). When the supply of respirators is limited a facemask is an acceptable alternative for routine interaction but a respirator

(preferably a powered or controlled air purifying respirator) should be worn for any aerosol generating procedures [82]. These procedures include intubation, cardiopulmonary resuscitation, and manual ventilation before intubation [44, 82]. Transesophageal echocardiography (TEE) has been included on this list; but the data is currently unavailable as to whether the risk of aerosolization during TEE is similar in both the setting of the paralyzed and intubated patient as opposed to the sedated patient without cuffed intubation who might be expected to gag or cough during the procedure. In light of this data gap, a conservative approach should be employed.

**Triaging elective cases and visits and limiting provider exposure:**

During this pandemic, patient to provider, provider to patient and provider to provider transmission represent major challenges. It is important to know that 3.8% of the cases reported from China were of healthcare team members suggesting that health care providers are at a significantly increased risk of contracting COVID-19 [11, 83]. This emphasizes the need for self-protection by all providers. This is especially a challenge in cases where PPE are limited and in emergent interventions such as cardiopulmonary resuscitation; providers should prioritize following PPE guidelines and should limit exposure. Similarly, elective and nonessential visits and procedures should be postponed. In the CHD settings, these include non-urgent cardiac surgeries, cardiac catheterization, TEE and electrophysiological procedures. Office visits can be postponed or scheduled through phone calls or telemedicine. Telemedicine technologies limit the patient and provider exposure while still allowing for patient care [44]. Teams must go through the exercise of considering unintended consequence to delayed access to care for the patient and put into place safeguards in their strategy. The duration of the corona virus pandemic is uncertain and therefore requires frequent reassessment of care plans. Specific definitions of urgent versus non-urgent should be created so that schedulers and care providers

are in alignment. The definition of non-urgent should include the concept that "delay of a certain duration unlikely to result in patient harm". Other strategies may include limiting the number of team members with exposure to suspected cases by allowing phone and chart review consults in patients admitted to the hospital. Most congenital cardiac centers hold weekly multidisciplinary conferences to discuss the cases and all team members including cardiologist, surgeons and anesthesiologists attend these conferences. Due to the requirement of social distancing to limit viral transmission management, and teaching conferences should be limited and virtual meetings should replace in person meetings (**Figure 2**)[84]. In addition, many hospitals are implementing staff screening strategies for symptoms and taking temperature for all employees and is assigning those staff non-essential for patient care to work remotely during these times. As age is a risk factor for severe disease, decisions must be made as to whether to restrict older physicians and care team members to work in settings with lower potential for exposure. In addition to the physical risks this is a stressful time for the care team members and it is important to keep provider wellness in mind. Resources can be found on the American College of Cardiology website and other professional societal websites [85]. During this time of "physical" distancing it is important to maintain "social connectivity" by supporting each other through our professional societies, our teams and our personal support networks. This has become increasingly via available video communication enterprises [85, 86].

**Education is needed**

New information is emerging every day on COVID-19. It is important to continue to follow the guidelines from the WHO, the CDC, your local health department, hospital and practice. It is also crucial to make this information easily available and accessible in real time and utilize data visualization tools to allow smooth transformation of the data to the public. In addition, social distancing has limited trainee education. Online education is now accessible and

resources from the ACC 2020 virtual national meeting will be available free of charge. Efforts to make other recorded material available for all providers are ongoing. Finally technology allows virtual meetings with video communications and conferences to allow for fellows teaching and continue to make multidisciplinary discussions accessible to all care team members.

**Gaps in Knowledge and Future Directions**

While data are emerging on COVID-19 effect on the cardiovascular system, there are several areas where further research is needed. Identifying high risk patients among children and adults with CHD is a priority. Furthermore, studies to understand the mechanisms of cardiovascular involvement in COVID-19 will facilitate the efforts to discover treatment options. In addition, several trials are ongoing searching for identification of the significance of the infection in patients with CHD, treatments and post exposure prophylaxis. An example is a collaboration effort between the Adult Congenital Heart Association and the International Society for Adults with Congenital Heart Disease in order to better understand the impact and burden of COVID-19 on adults with CHD in the United States and globally.

**Conclusion**

During these trying times of COVID-19 pandemic, cardiovascular team members will play a central role in controlling the disease. Patients with CHD are likely to become increasingly affected with COVID-19 and may have more grave outcomes than other populations during the pandemic due to their perturbed physiologic state and co-morbidities. Infection control processes are crucial. Continuing research and education about the disease may provide us with insights to alleviate morbidity and mortality in the near future.

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**Table 1. The Anatomical and Physiological (AP) Class for Adults with Congenital Heart Disease Considered at Higher Risk for Corona virus Disease of 2019 (COVID-2019) (AP Class IB-D, IIA-D and IIIA-D).**

| |
|---|
| **I: Simple**<br>Includes simple native lesions (isolated small ASD or VSD, mild isolated pulmonary stenosis) or repaired lesions (ligated or occluded PDA), repaired ASD or VSD without residual shunting or chamber enlargement. |
| **II: Moderate complexity**<br>Repaired or unrepaired lesions including AVSD, aortic or mitral valve disease and coarctation of the aorta, anomalous pulmonary venous return, ALCAPA, AAOCA, Ebstein, TOF, PS (moderate or greater), VSD with moderate or greater shunt. |
| **III: Great Complexity (or Complex)**<br>Cyanotic congenital heart defect (unrepaired or palliated, all forms), double-outlet ventricle, Fontan procedure, IAA, single ventricle, TGA (classic or d-TGA; CCTGA), truncus arteriosus |
| **A:** NYHA FC I symptoms, no hemodynamic or anatomic sequelae, no arrhythmias, normal exercise capacity, normal renal/hepatic/pulmonary function |
| **B:** NYHA FC II symptoms, mild hemodynamic sequelae (mild aortic enlargement, mild ventricular enlargement, mild ventricular dysfunction), Mild valvular disease, Trivial or small shunt (not hemodynamically significant), Arrhythmia not requiring treatment, Abnormal objective cardiac limitation to exercise |
| **C:** NYHA FC III symptoms, significant (moderate or greater) valvular disease; moderate or greater ventricular dysfunction (systemic, pulmonic, or both), moderate aortic enlargement, venous or arterial stenosis, mild or moderate hypoxemia/cyanosis, hemodynamically significant shunt, arrhythmias controlled with treatment, pulmonary hypertension (less than severe), end-organ dysfunction responsive to therapy |
| **D:** NYHA FC IV symptoms, severe aortic enlargement, arrhythmias refractory to treatment, severe hypoxemia (almost always associated with cyanosis), severe pulmonary hypertension, Eisenmenger syndrome, refractory end-organ dysfunction |

The classification includes a number for the anatomical classification and a letter for the physiological classifications. Examples are included in table. AAOCA: Anomalous aortic origin of the coronary artery, ALCAPA: anomalous origin of the left coronary artery from the pulmonary artery, ASD: atrial septal defect, AVSD: atrioventricular septal defect, CCTGA: congenitally corrected transposition of the great arteries, FC: functional class, NYHA: New York Heart Association, PDA: patent ductus arteriosus, PS: pulmonary stenosis, TOF: tetralogy of Fallot, TGA: transposition of the great arteries, VSD: ventricular septal defect.

**Table 2. Lesions with Congenital Heart Disease Potentially at High Risk of Severe Corona virus Disease of 2019 (COVID-19) [63].**

| Lesion and Category | Reason for Vulnerability |
|---|---|
| **Single Ventricle Patients Status Post Fontan Operation** | Passive pulmonary blood flow which is dependent on pulmonary vascular resistance. Hypoxia can lead to elevated pulmonary pressures and low cardiac output Ventilated patients requiring high PEEP at risk for low cardiac output. |
| **Patients with chronic cyanosis (Saturation <85%)** | Respiratory disease will lead to more profound cyanosis due to pulmonary venous desaturation. These patients may require to be admitted for respiratory support Erythrocytosis increases the risk of thrombosis and COVID-19 disease may also increase the risk in thrombosis |
| **Severe cardiomyopathy requiring medications or depressed cardiac function in congenital patients** | COVID-19 may worsen ventricular function and result in heart failure symptoms. The viral sepsis will also increase metabolic demand and unmask heart failure in these patients |
| **Severe pulmonary hypertension** | Respiratory illness will result in increased pulmonary vascular resistance and may lead to pulmonary hypertension exacerbation, right heart failure and low cardiac output |
| **Post heart transplantation** | Immunosuppression and the immune response may lead to worse COVID-19 infection or potentially graft rejection in the course of the disease |
| **Infants with unrepaired congenital heart disease like tetralogy of Fallot, ventricular or atrial septal defects** | Depending on the physiology these patients may have a large left to right shunting or a degree of cyanosis. Respiratory infection will worsen cyanosis and large left to right shunt increase the risk for respiratory illnesses |
| **Preexisting non-cardiac conditions and syndromes that may result in reduced immunity** | Patients with chronic kidney or lung disease or cancer and congenital heart disease have multiple organ vulnerabilities and are considered high risk. Also patients with 22 q 11, Down syndrome, CHARGE syndrome or patients who lack a functional spleen (heterotaxy patients) should be considered high risk for COVID-19 due to the theoretically impaired immune response. |
| **Adult CHD patients with known coronary artery disease and systemic hypertension** | The data that is available thus far indicates that systemic hypertension and the presence of coronary artery disease are significant risk factors for mortality with COVID-19. |

CHD: congenital heart disease.

**Table 3. Medications and Corona virus Disease of 2019 (COVID-19).**

| Medication | Potential Concerns and Suggestions |
|---|---|
| **Aspirin** | Theoretical concern for Reye syndrome although the only reports were at high doses used in Kawasaki disease in the setting of influenza or varicella. No reports with COVID-19. Suggest continuing Aspirin. |
| **ACEi/ARB** | Theoretical concern due to potential upregulation of ACE-2. No data to support an interaction with the disease. Suggest continuing the medication. |
| **Anticoagulant medications** | COVID-19 may cause DIC and coagulation cascade abnormalities in severe cases. Suggest continuing the medication in mild cases and adjust as needed in severe cases. |
| **NSAIDs** | Some clinician suggested worsening course of the disease if given early. There is no data to show any association of NSAIDs with the course of the disease. The WHO does not recommend avoiding NSAIDs. |
| **Digoxin and Nitroglycerine** | There is no information to suggest any harmful effect in COVID-19 patients thus it is reasonable to continue these medications. |
| **COVID-19 potential treatments (antivirals, antimalarial and other medications)** | Each medication should be evaluated in light of the available evidence and potential interactions with the current medications the patient is taking. In addition some of these medications can prolong the QT interval and this should be taken into consideration especially in patients on other QT prolonging agents. |

ACE: angiotensin converting enzyme, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, NSAIDs: Nonsteroidal anti-inflammatory drugs, COVID19: Corona virus Disease of 2019.

**Figure Legends:**

**Figure 1. Suggested measures to reduce exposure to Corona virus Disease of 2019 (COVID-19) pandemic.**

**Figure 2. The Power of Social distancing to decrease the spread of Corona virus Disease of 2019 (COVID-19) and staying connected at the time of pandemic.** Left panel without social distancing one person infects ~ 400 and the number decreases to 15 with 50% less exposure in 30 days [84].

## Reducing Exposure During COVID-19 Epidemic

At phone triage

- Cancel all non-urgent visits
- Use phone visits and telemedicine if possible
- Screening for exposure and respiratory symptoms for all patients coming to the facility

At registration if symptomatic

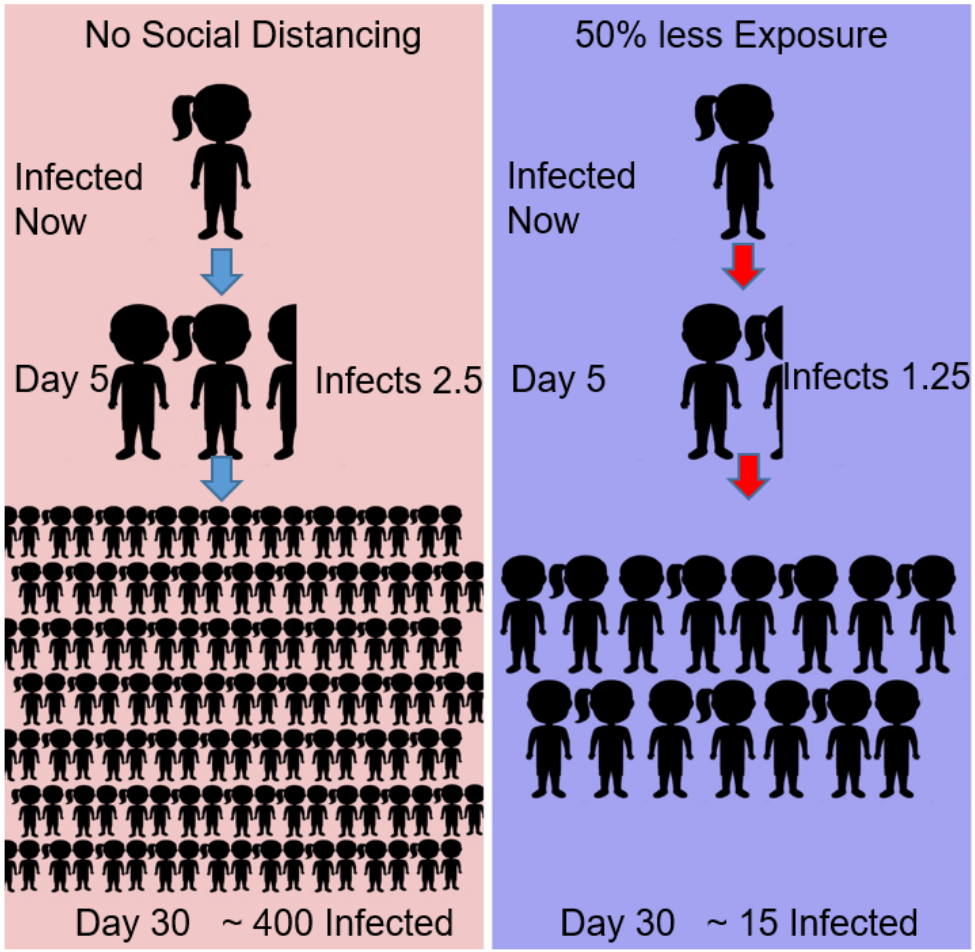
- Provide mask to patient and family
- Ideally separate waiting rooms
- Complete exposure/travel screen and assign to an isolation room

At clinical evaluation if symptomatic or confirmed exposure

- Use a respirator or a facemask, gloves, gown and eye protection
- Use a respirator (e.g.N95), gloves, gown and eye protection for aerosol generating procedures

At disposition for suspected COVID-19 patients

- Home: recommend self quarantine for 14 days. Testing per local policy
- Admission: special isolation unit until testing results are back


No Social Distancing
Infected Now
Day 5
Infects 2.5
Day 30 ~ 400 Infected
50% less Exposure
Infected Now
Day 5
Infects 1.25
Day 30 ~ 15 Infected