

## Resilience and response of the congenital cardiac network in Italy during the COVID-19 pandemic

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**The worldwide response to the current COVID-19 pandemic has been focused on how to prevent the disease and to protect the high-risk patient from a potentially lethal infection. Several consensus and guidelines articles have been published dealing with the cardiac patient with systemic hypertension, heart transplant or heart failure. Very little is known about the patients, both in the pediatric as well as in the adult age, with congenital heart disease. The peculiar physiology of the heart with a native, repaired or palliated congenital heart defect deserves a specialized care. Hereby we describe the early recommendations issued by the Italian Society of Pediatric Cardiology and Congenital Heart Disease and how the network of the congenital cardiac institutions in Italy reacted to the threat of potential wide spread of the infection among this fragile kind of patient.**

On 11 March 2020, the worldwide outbreak of coronavirus infection (COVID-19) was definitively recognized as a pandemic disease by the WHO<sup>1</sup> and in few weeks the toll of sick patients rapidly expanded, with more than 1500 000 confirmed cases and 94 807 deaths as of 9 April 2020 (these data are largely underrepresenting the actual size of infected population worldwide).

The clinical feature of the COVID-19 disease is heterogeneous ranging from asymptomatic patients to dramatic acute respiratory distress syndrome with high mortality burden among older patients or those with underlying comorbidity. While respiratory failure was originally deemed as the main factor leading to morbidity and mortality, primary cardiac involvement is gradually emerging as another important player within the clinical spectrum of COVID-19 infection,<sup>2,3</sup> leading to arrhythmias,<sup>4</sup> cardiac troponin-I elevation due to cytokine storm,<sup>5</sup> stress-induced myocardial dysfunction or even acute myocarditis.<sup>6,7</sup> Most importantly systemic endothelial dysfunction is increasingly recognized as a key player in developing target organ dysfunction and life-threatening thromboembolic events.

The COVID-19 crisis prompted all the major scientific societies to release recommendations aimed at driving

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the care of infected patients at high risk due to cardiovascular comorbidities, as well as to guide treatment and hospital access to patients with acute cardiac illness but without, or even unknown, COVID-19 status. Among many others, the European Society of Cardiology (ESC) and the American College of Cardiology and American Heart Association (ACC/AHA) provided updated position papers concerning priority for emergency catheterization laboratory access,<sup>8,9</sup> health workers protection<sup>8,10</sup> and indications for urgent structural interventions.<sup>11</sup> Resource utilization is another critical point, especially if considering that ExtraCorporeal Mechanical Circulation (ECMO) support, a potentially life-saving procedure in profound hypoxemic patients despite invasive mechanical ventilation,<sup>12</sup> yielded disappointing results in COVID-19 patients,<sup>13</sup> nonetheless leading cardiothoracic surgeons enter the fray in fighting the pandemic.<sup>14,15</sup>

While attention has been focused on the patient categories most jeopardized by the COVID-19 outbreak, like the elderly patient with cardiac comorbidities, or the one needing urgent coronary/structural interventions or even those waiting for heart transplantation,<sup>16,17</sup> only a few articles have been dedicated to the patients with congenital heart disease, mostly on the issue of resource utilization and decision-making about indication for invasive

procedures<sup>18,19</sup> and planning in patients needing cardiac surgery.<sup>20</sup> At the beginning of March 2020, after the coronavirus had spread out of the Chinese borders, Northern Italy was heavily struck by the violent pandemic outbreak of COVID-19, claiming more than 25 000 deaths as of 26 April. Moreover, before effective lockdown countermeasures could be implemented, several people moved out of the northern cities during the early stages, thus potentially spreading out the infection over the whole country. In this context, the response to the crisis was multifaceted. Some cardiology and cardiac surgery units (mostly those in Northern Italy) were forcibly converted to the care of severely sick COVID-19 patients, thus waiving any kind of emergency, urgent or elective procedures on patients with congenital heart disease. In Lombardy, urgent care or transplant candidates have been referred, in a hub and spoke system decreed by the regional government, to a unique hospital outside the epicenter of the COVID-19 crisis and which acted as a hub for the congenital cardiac population (IRCCS Policlinico S. Donato, Milan). Another 'COVID-19 free' hub was the Ospedale Bambino Gesù, Rome, which collected patients from some centers in Southern Italy which had been entirely devoted to the COVID-19 emergency, and acted as a transplant-ECMO-Ventricular Assist Device (VAD) backup institution, in a dedicated building outside the main hospital, with intensive care facilities. All the other congenital cardiac institutions, apart from the Monaldi Hospital in Naples, were able to provide both an enclave for noninfected patients as well as a COVID-19-dedicated section. The safeguard of these 'COVID-19 free' institutions was warranted by locally and independently drafted rules, regulating the admission and care of the incoming patient, and were not the result of a nationally standardized care program. Generally, all patients had coronavirus swab tests in safe areas before being admitted to the ward. Occasionally, patients deemed at high risk for COVID-19 infection (i.e. those coming from highly infectious areas or with known previous contact with other infected individuals) were put on a 14-day-long quarantine if the cardiac conditions had been stable enough. Other centers shut down any elective activity while retaining the capacity for dealing with the necessity of urgent surgical treatments (neonatal palliative procedures or urgent repair, ECMO etc.) or invasive cardiology procedures (Rashkind septostomy, urgent balloon valvuloplasty etc.). Currently, we have no information about the type and number of procedures which have been carried out during the COVID-19 pandemic, but a delay in the care of out-of-hospital medical emergency situations, as it was recently described for adult patients, is very unlikely. This is because congenital cardiac patients are usually tightly connected to their referral institution and experience a relatively low rate of unexpected cardiac emergencies. The outpatient clinic was either completely abolished or maintained for the most urgent and frail patients, following strong triage protocols and nasopharyngeal swab test if available. In

summary, despite having major national hubs for congenital patients in Northern and Southern Italy, the decision whether to limit or even close congenital cardiac activity was made entirely on a local or regional basis, and no specific directive was ever issued by the National Health Ministry.

The Italian Society of Pediatric Cardiology and for Congenital Heart Disease recently posted recommendations to all members, based on the evidence collected by the major Italian congenital cardiac care institutions, together with the currently available data in the literature, which is the subject of the current report.

### **Triage and general prevention**

Elective procedures should be postponed until a safe environment can be provided in terms of access to the hospital as well as protection toward contamination of 'COVID-19 free' enclaves by scrupulous preemptive virus testing, even if early infected asymptomatic patients may go unnoticed.<sup>21</sup> Emergency and urgent cardiological and surgical procedures should be carried out providing maximum operator safety.<sup>9,10,20,22</sup> Outpatient clinics should be limited to high-risk patients (cardiac failure, pulmonary hypertension, transplant recipients), emphasizing adequate distancing and appropriate scheduling. The pediatric cardiologist in charge of the outpatient clinic is responsible for assigning priority codes for patients scheduled for visit and for implementation of phone/social network at home monitoring of less urgent cases. The creation of a network of dedicated telemedicine equipment is gaining wide acceptance as a potent tool for monitoring and even at-distance treatment and should be encouraged.<sup>23</sup> Personal protective equipment should be available as needed and as elsewhere described.<sup>9</sup> At this stage of knowledge, routine nasopharyngeal swabs to diagnose infected patients before admission seem reasonable, but the role of serology study to improve patient streaming and reduce viral spreading is still unclear.

### **Neonates, infants and children with congenital heart disease**

As far as is currently known, the pediatric age seems to be partially protected from the occurrence of the typical respiratory distress syndrome caused by COVID-19 infection,<sup>24,25</sup> with an overall milder clinical course.<sup>26</sup> Less than 1% of the children who had positive swabs developed severe signs of respiratory distress or multiorgan failure,<sup>25</sup> in stark contrast to the 5% rate as reported for adult patients. Nevertheless, the inherent frailty of the congenital heart patient should not be overlooked, since imbalance between the pulmonary and the systemic circulation, cyanosis and myocardial dysfunction are common traits of this kind of patient, often in a combined fashion. Pediatric patients with congenital heart disease presenting with any kind of complicated set of symptoms (Table 1) should be regarded as potentially COVID-19 infected.<sup>27</sup>

**Table 1 Factors associated with high-risk COVID-19 infection in patients with congenital heart disease**

1.	Abnormal respiratory rate (more than 50 bpm between 2 and 12 months of age; more than 40 bpm between 1 and 5 years of age; more than 30 bpm above 5 years of age)
2.	Fever persisting for more than 3–5 days
3.	Neurological disorders
4.	Elevation of creatine-kinase MB, decreased lymphocytes, leucopenia and elevated procalcitonin
5.	Metabolic acidosis
6.	Typical radiographic presentation for interstitial pneumonia
7.	Pulmonary bacterial infection

Patients with shunt-dependent pulmonary circulation, especially neonates and infants after Norwood stage I procedure or with chronic reduction of pulmonary flow and significant cyanosis with saturation persistently less than 85% (mostly those with severe peripheral pulmonary stenosis, undersized systemic-to-pulmonary shunt etc.), should be considered as the population at the highest risk and deserve constant monitoring. Early aggressive treatment should be warranted, in the event of suspected coronavirus infection, by a dedicated respiratory/cardiovascular care team in a COVID-19 prepared institution. Mildly symptomatic or well compensated patients with a high Qp/Qs ratio (atrial and ventricular septal defects, atrioventricular canal defects, medium sized patent ductus), while taking benefit from the overall safety settings, should be probably considered at a reduced risk in case of COVID-19 infection. For these patients, interventional or surgical repair should be postponed until a safe environment can be provided and unless there is no risk of developing irreversible pulmonary vascular disease. For what concerns urgent and undeferrable procedures, the joint Society of Thoracic Surgeons/American Association of Thoracic Surgeons/Congenital Heart Surgeons Society (STS/AATS/CHSS) document<sup>20</sup> makes a clear and acceptable statement. Atrial septostomy, balloon dilatation of critical pulmonary/aortic stenosis and any emergent/urgent postsurgical procedure in the catheterization laboratory should not be postponed. Stabilization, either surgically or by catheter intervention, of patients on prostaglandin E infusion for duct-dependent disease is recommended.

Neonates born from COVID-19-positive mothers should be treated as potential virus carriers, since vertical transmission of the infection has not been definitively ruled out. Indeed, despite early reports showing a very low risk of mother-to-fetus transmission,<sup>28</sup> IgM antibodies have been recently found in a neonate born from an infected mother.<sup>29</sup> Urgent surgical or interventional procedure should not be delayed in these cases, but great care must be taken to avoid possible contamination of the COVID-19-free enclave.

### Patients with single ventricle physiology after Glenn/Fontan procedures

This is a quite peculiar subtype of population. Interstitial pneumonia within a central venous pressure driven

pulmonary circulation is a most worrisome condition and the negative impact of positive pressure ventilation on pulmonary blood flow and cardiac output (CO) in patients with cavopulmonary connection is well known. Moreover, the recognition of a potential hypercoagulable state in patients affected by coronavirus infection<sup>30,31</sup> poses a threat to patients whose pulmonary blood flow and CO rely on as low as possible vascular resistance values. However, their use of low molecular weight heparin as prophylactic anticoagulation is still controversial<sup>32</sup> and patients on antiaggregation/anticoagulation medications should not modify their therapy. It is reasonable to promote enhanced security actions to avoid infections among these patients.

### Patients with dysfunction of the systemic ventricle

It is now clear that, besides the effect of adding respiratory distress to a borderline compensated cardiovascular system, the coronavirus infection has a direct impact on cardiac myocytes by exploiting the angiotensin converting enzyme 2 to enter human cells.<sup>6,33</sup> The clinical presentation may vary from simple yet unnoticed transient elevation of troponin levels up to the onset of severe systolic ventricular dysfunction with reduced ejection fraction.<sup>34,35</sup> Pediatric patients who are on follow-up for an otherwise stable dilative cardiomyopathy, or any other kind of systolic impairment of the systemic ventricle, who present with fever, cough, elevated serum troponin, NT-proBNP as well as D-dimer and inflammatory biomarker elevation, should be regarded as high-risk individuals for being under COVID-19 disease. There are still no clues as to whether endomyocardial biopsy should be undertaken in these patients, albeit it may be appropriate in selected cases<sup>6</sup> with or without previous magnetic resonance imaging study, depending on the institutional policy, if anti-inflammatory or any other kind of compassionate experimental therapy is planned. Management of these patients should be the standard protocol with inotropes, vasopressors and diuretics as usual.

### The adult congenital cardiac patient

Since patients with underlying cardiovascular disease are at higher risk of morbidity and mortality, adults with congenital cardiac disease should be instructed on how to minimize the risk for infection. Based on the AHA/ACC 2018 guidelines for congenital heart adults,<sup>36</sup> any patient with complex congenital heart disease or with NYHA class from II to IV should be considered at high risk for complications related to COVID-19 infection (specifically for patients in physiologic class C and D). All the previously described threats may apply to the adult congenital patient and special attention must be paid to those with pulmonary hypertension and with Eisenmenger syndrome. There is no current evidence of the impact of the coronavirus pandemic on pulmonary hypertension patients, but several national health agencies

(NHS-Pulmonary Hypertension Association UK, Center for Disease Control, Atlanta) and pulmonary hypertension-related associations provide general guidelines on safety and prevention with emphasis on social distancing. Management should be undertaken as usual in every patient with pulmonary hypertension, but it is reasonable that inhaled nitric oxide therapy might be most beneficial to overcome the crisis, while intravenous pulmonary vasodilators should be used with caution due to the risk of ventilation/perfusion mismatch and worsening cyanosis.<sup>37</sup> Older patients with Fontan palliation should also be considered at increased risk, when compared with children, due to the progression of multiorgan dysfunction (hepatic, renal) and age-related increase of pulmonary vascular resistances consistent with the chronic trade-off of the cavopulmonary circulation.<sup>38</sup>

### Patients with cardiac transplant

There has been a lot of concern, at the onset of the COVID-19 pandemic, about the impact of this viral illness while on immunosuppressive therapy due to previous heart transplantation. Since these patients, albeit being former congenital cardiac patients, are being followed by posttransplant dedicated teams, it is not in the scope of this article to bring details among this kind of population. Pediatric cardiac transplant receivers usually share the same problems with the adult population and current data may suggest a milder course of COVID-19 due to a reduced host-inflammatory response, possibly due to the concomitant use of immunomodulatory drugs.<sup>17,39,40</sup>

### Therapeutic options and interaction with cardiac medications

There are no specific recommendations for patients with congenital cardiac disease for what concerns medical therapy. At the beginning of the pandemic, there was some worry about the potential harm of angiotensin-converting-enzyme inhibitors, as these drugs may enhance virus adhesion to the target cell surface, thus promoting the infection. However, current guidelines as well as the available data<sup>41</sup> do support the continued use of vasodilator therapy in patients with heart failure. The interplay between the COVID-19 infection and the common medical therapies in patients with congenital heart disease is still unclear. Children and young patients with heart defects are known to display a high prevalence of QT duration and ventricular repolarization abnormalities, particularly after cardiac surgery. In this setting, the prophylactic use of hydroxychloroquine should be cautious.<sup>42</sup> Steroids play an interesting role, since they have been considered as a potential risk factor for facilitating the infection at the very early stages of the pandemic. However, the unscathed story of transplant patients as well as the prompt recovery induced by generous doses of steroids and intravenous immunoglobulin, in cases with coronavirus-related Kawasaki-like disease due to a diffuse systemic vasculitis,<sup>43</sup> clear the use of steroids as a mainstay against

this potential mid-term immune-mediated complication. An increased risk for thrombotic complications has been reported in Covid-19-affected patients, but we have no clues about the potential impact of coronavirus infection on congenital cardiac patients while on anticoagulation or antiplatelet drugs, which should of course be continued if indicated. Similarly, no proof to recommend the prophylactic use of remdesivir in this kind of patient. The use of ECMO has been regarded as a potential life-saving tool and thus been advocated in the critical COVID-19 patient.<sup>14,44,45</sup> However, a word of caution has been raised due to the inherent problems of extracorporeal mechanical support in septic patients and the problems facing venoarterial support in the setting of a dysfunctional systemic ventricle. Moreover, the peculiar anatomy and physiology of the heart in several kinds of congenital malformations, both native as well as after surgery, adds further complexity to an already difficult setting. Since the costs and availability of the resource-intensive ECMO equipment and management are another matter of concern, ECMO of congenital cardiac patients with overlying COVID-19 infections should be prioritized to centers with recognized experience in congenital cardiac cardiology and surgery.

### Concluding remarks

The COVID-19 pandemic has an important impact on the health system of several nations. In Italy, the overall mortality was very high, with the most vulnerable patients, the older ones and those with severe comorbidities, carrying the highest toll. Predicting a disaster among the population of fragile neonates with complex congenital heart disease, or the adult with a Fontan procedure, or the one with Eisenmenger disease, was easy. On the contrary, there was no reported death<sup>46</sup> and the swift institution of 'COVID-free' dedicated areas with congenital cardiac surgery and cardiology expertise helped to reduce the risk of the infection spreading within this particular community. It is unclear at this stage whether treatment of pediatric patients with COVID-19, pneumonia and cardiac comorbidities should include upstream use of hydroxychloroquine or chloroquine, macrolide antibiotics and/or protease inhibitor (such as it has been implemented for adult patients). Clinicians must discuss potential risks and benefits of treatment, data on outcomes needs to be collected, the patient's condition must be severe and the drug cannot be in short supply.

Moreover, the number of patients with congenital heart disease and COVID-19 infection is underrepresented, probably due to the habit of social isolation during periods of contagious viremia such as flu. The next frontier will be the reprise of the ordinary care and elective surgical and cardiological procedures for all patients while maintaining safety barriers and constant attention against the potential recurrence of generalized infection. A shared multiinstitutional plan for a coordinated response to major crises jeopardizing

the care of patients with congenital heart disease is warranted.

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### Conflicts of interest

There are no conflicts of interest.

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