EFFECTS OF COVID-19 ON CHILDREN

Direct and indirect effects of the COVID-19 pandemic on children with cardiovascular disease

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ABSTRACT

Coronavirus 2 (SARS-CoV-2) the causative agent of what we now know as "Coronavirus Disease 2019" (COVID-19), is the most serious global health crisis of our generation, with a significant and far-reaching impact upon health, economy, social cohesion and emotional and mental wellbeing. Although children do not bear the brunt of direct mortality, they are significantly affected in terms of morbidity and interruption to access, continuity and complexity of care, as well as the indirect social and financial effects impacting on their health outcomes. In this review we present some of the most recent data relevant to children with congenital and acquired heart disease, and consider some of the cardiac presentations noted. We discuss the necessary protections to staff in the echo and cardiac catherisation laboratories and present some general recommendations to general paediatricians and communities to ensure the continued health of our patients. Finally, we encourage ongoing registries and biorepositories and support clinical trials to ensure that children also receive new technologies and therapeutics as these become available.
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INTRODUCTION

On 31 December 2019, the World Health Organization (WHO) reported a cluster of pneumonia cases in Wuhan City, China. The majority of the patients initially identified were dealers and vendors at a seafood, poultry and live wildlife market in that area. "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2) was confirmed as the causative agent of what we now know as "Coronavirus Disease 2019" (COVID-19). Since then, the virus has spread to 213 countries and territories around the world with a total of 6 177 120 confirmed cases and a death toll of 371 287 deaths as of 31 May 2020.[1] At the beginning of the pandemic, travellers to areas with ongoing sustained transmission of COVID-19 were at greatest risk of infection, but it has now extended to local and community transmission. Furthermore, the elderly, individuals with co-morbidities, especially cardiovascular disease,[2] and healthcare workers have been found to be at a higher risk of death. We are in the midst of the most serious global health crisis of our generation, with a significant and far-reaching impact upon health, economy, social cohesion and emotional and mental wellbeing.

In a recent systematic review of the ever-increasing literature, 45 relevant scientific papers and letters noted that not only have children so far accounted for only 1% - 5% of diagnosed COVID-19 cases, they also have milder disease than adults and deaths have been extremely rare. Although diagnostic findings have been similar to adults, with fever and respiratory symptoms being prevalent, fewer children seem to have developed severe pneumonia, elevated inflammatory markers were less common in children, and lymphocytopenia seemed rare.[3] New-born

infants have developed symptomatic COVID-19, but evidence of vertical intrauterine transmission is scarce.[4] Even in high mortality communities, such as China, Italy and Spain, the low incidence in children and decreased mortality and improved outcomes have been sustained. However, the paediatric population in South Africa have differing clinical characteristics and profile, with possible implications for risk in this population. Of interest, in particular, are children with underlying immune compromising illness such as HIV and TB, underweight and malnourished children, and those with underlying chronic medical conditions.[5] As the South African paediatric cardiology community, we are deeply concerned as the impact of SARS-CoV-2 – both directly and indirectly – is as yet unknown. The complete clinical picture with regard to paediatric COVID-19 is still not fully clear and nuances in children have not been comprehensively reported or defined.[6] Atypical presentations in children include a Kawasaki-like picture and unusual cutaneous lesions.[7-11]

Treatment currently is only supportive with no specific antiviral treatment available. There are few data regarding treatment with adjunctive therapies such as steroids, hydroxychloroquine, intravenous immunoglobulins amongst others in children, and there is a real need for evidence-based directed therapies, interventions and medical management. In a review of 1 391 children tested for COVID-19 in Wuhan, China, a total of 171 (12.3%) were confirmed to have SARS-CoV-2 infection. Outcomes were good with only one mortality.[12] As children in our setting have vastly different socio-economic backgrounds to these children, with potential effects from HIV-exposure and infection and a high TB prevalence rate, it is critically important to review our population, their outcomes and consider contextualised treatment and management strategies. This manuscript, prepared prior to seeing large numbers of children with COVID-19, reviews some of the literature to date, focusing on some of the clinical presentations relevant to our speciality, considers some of the potential areas of impact on our patients, suggests intervention and protection measures, and concludes with final suggestions to our community and to general paediatricians/practitioners and patients.

BACKGROUND

Very few children have a poor outcome following SARS-COV-2 infection. Shekerdemian and colleagues reported the North American paediatric intensive care experience during a three week period in March 2020.[13] Only 48 patients were collected from 46 participating units, 73% of these children had a respiratory illness and 40 of the 48 had underlying medical conditions. Only 2 of this cohort died during the period under review. "Adult" risk factors such as obesity also applied to these younger individuals. There are too few data available to establish whether underlying heart disease in children confers an increased risk of developing severe COVID-19.

Recently, during the decline in the new infection phase in areas of major outbreaks, reports of unusual presentations involving the cardiovascular system in children have appeared. Italian authors reported that patients with Kawasaki disease (many associated with documented coronavirus infection) were seen 30 times more commonly in the North of Italy in the first few months of 2020 than in the 5 previous years.[14] Ten patients were described. They were generally older than typically reported, with a median age of 7.5 years. Half of the children had typical Kawasaki disease, and half were reported as having "Kawasaki shock syndrome" (KSS) with hypotension as part of the presentation. Five children had "macrophage activation syndrome" (MAS). Three children had both KSS and MAS.

A more severe illness attributed to a cytokine storm similar to that seen in adults was also noted to be occurring in children (sharing features seen in the Italian publication) in April 2020. Frustratingly for health personnel, the reports appeared simultaneously in the lay press and societal bulletins, before details emerged in scientific journals. Fortunately, the facilitation of information sharing from professionals in affected areas following the widespread use of easy-to-use videoconferencing software (arguably one of the few benefits of lockdown), has countered the lack of information in the professional press. A number of terms – multisystem inflammatory syndrome in children (MIS-C), paediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2 (PIMS-TS) and paediatric COVID-associated Multi-system Inflammatory Syndrome (PMIS)[15-17] – have been applied to the acute and potentially life-threatening illness typified by a delayed presentation with hypotension rather than respiratory illness. The condition has been associated with few deaths, however a few patients have required extracorporeal membrane oxygenator support in order to survive.[18] Therapy of patients has included the use of inotropic support, immunoglobulin infusions, high dose steroids and the recombinant IL-1 receptor antagonist Anakinra.[19]

Much information can be gleaned from short case series or individual case reports.[20,21] While patients with typical "Kawasaki like illness" are described,[20] more patients have been described who present with gastrointestinal symptoms, troponin leak and cardiac dysfunction and thrombocytopenia, which are not as commonly described in KSS.[21] These patients often do not have a respiratory illness and do not have viral RNA detected in respiratory secretions; evidence of corona-

virus infection is determined by the presence of antibodies to SARS-COV-2.[17]

These features have prompted Stanford Shulman, the distinguished infectious disease expert, to opine that while the occasional patient has true Kawasaki disease, the majority of children presenting with the severe illness after infection have a similar illness to adult patients who have been described as having a cytokine storm.[17]

MYOCARDIAL INVOLVEMENT

There are few data available specifically regarding myocardial involvement in children with COVID-19 infection. The Chinese Centre for Disease Control and Prevention reported 2% out of 72 314 cases infected by the COVID-19 virus were less than 19 years of age.[22]

The SARS-CoV-2 virus has a similar binding domain to SARS-CoV which attaches to human cells after binding to angiotensin converting enzyme 2 (ACE2), a peptide which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.[23,24] ACE2 has a similar structure to angiotensin converting enzyme (ACE), but unlike ACE is responsible for the cleavage of Angiotensin II into metabolites that have vasodilatory, anti-fibrotic and anti-hypertrophic roles. ACE2 also has immunomodulatory properties indirectly reducing angiotensin II, which tends to cause inflammation. Downregulation of ACE2 activity occurs once binding to cells is complete. ACE 2 has a protective role and heightened angiotensin II activity secondary to its down regulation may be a mechanism leading to cardiac and/or lung injury in COVID-19 infections.[24]

Several significant differences in the frequency of distribution of ACE2 variants among different racial and ethnic lines have been described. Serum levels of ACE2 have also been negatively correlated with body mass index, pulse pressure, and oestrogen levels.[25] There is a cardio-protective effect of circulating ACE2 and oestrogen participates in the upregulation of ACE2 activity levels, which may explain the susceptibility of males to COVID-19.[26] Children also have higher levels of ACE2 than adults.[27] ACE2 can pass through the placenta, enabling the mother to transfer to her baby her immunity and other forms of protective soluble factors.[28]

Overt involvement of the myocardium in children is uncommon and has been suggested by the presence of elevated myocardial enzymes which were shown in 31% of 36 children as part of routine laboratory testing in one study.[28] Leukopenia, lymphopenia, and increased myocardial enzymes were noted in both children and adults with a similar frequency. Adult patients, however, showed an increased C-reactive protein response compared with children, suggesting a milder immunological response in children.[28]

The manifestation of myocardial injury in adult patients with COVID-19 has been shown to vary in severity. Some patients are asymptomatic and may only be detected by laboratory markers such as raised cardiac troponin levels, which if very elevated, is prognostic for in-hospital mortality. Myocardial involvement has been shown to manifest clinically with chest pain caused by myocardial ischaemia or myocarditis, palpitations and acute heart failure. Heart failure is commonly associated with cardiovascular comorbidities, and is frequent in patients who die with COVID-19 infection.[29,30]

Few cases with confirmed myocarditis and COVID-19 infection have been reported. Endomyocardial biopsies have shown that the virus can be present, but may not necessarily have a pathogenic role in some cases.[31] An indirect method of myocardial injury related to an inflammatory or oxidative stress in the setting of COVID-19 infection is suggested in the case of reversed Takotsubo cardiomyopathy, where the endomyocardial biopsy (EMB) showed a diffuse T-lymphocytic inflammatory infiltrate associated with limited focal necrosis without the SARS-CoV-2 genome being detected. An alternative explanation for the absence of finding the virus present is that EMB has a potential sampling error. It is likely that with more autopsy evidence, COVID-19 related viral myocarditis may emerge.[24,32-34]

EFFECTS ON THE CONDUCTION TISSUE

An indirect effect on the conduction tissue in patients with COVID-19 infection has been documented with treatment using hydrochloroquine, which has antiviral efficacy against SARS-CoV-2. The combination of azithromycin and hydrochloroquine has a synergistic effect and is associated with severe QT prolongation and the potential for torsade de pointes.[34] A recent systematic review was unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19.[35] However, each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19. Cases of bradyarrhythmias have been documented in adult patients, including sinus node dysfunction[36] and transient complete heart block.[37]

Myocardial and conduction tissue involvement may become more evident as the COVID-19 pandemic evolves and more children become infected. Although children seem to be

protected and experience mild symptoms, the possibility of myocardial involvement with associated ventricular dysfunction and dysrhythmias should not be overlooked.

THE IMPACT ON CONGENITAL HEART DISEASE IN SOUTH AFRICA

Accurate birth and community prevalence of congenital heart disease (CHD) is lacking in South Arica. Estimating from current live birth rates, approximately 2 500 children with significant CHD requiring intervention are born annually, contributing to the considerable pool of patients with "corrected", palliated, uncorrected and undetected CHD within communities in the country.

Current consensus is that in the vast majority of cases of children infected with SARS-COV-2 are asymptomatic or mildly symptomatic.[3,38,39] Available information suggests that children with underlying conditions appear to be among those at higher risk of severe disease. The numbers of those becoming seriously ill and requiring hospitalisation are, however, still far fewer than adults with cardiovascular disease and the specific risk for CHD remains unclear.

Extrapolating from experiences with seasonal viral illnesses, the best studied being RSV,[40] COVID-19 infection would be expected to have more serious manifestations in haemodynamically significant congenital heart disease. Expected presentations include:

- Increasing respiratory distress in conditions that manifest with heart failure – left to right shunts such as ventricular septal defects, patent arterial duct and more complex common mixing conditions. Hepatomegaly and cardiomegaly – both clinically and radiographically, should alert the clinician to a cardiac cause. Cardiac murmurs are not always prominent, particularly in patients with the largest shunts and associated pulmonary hypertension. The lung changes caused by pulmonary plethora or pulmonary venous congestion may not always be differentiated by a primary care physician from that of COVID-19 or other disease processes.
- Increasing cyanosis or hypercyanotic episodes: Deterioration could be expected in patients with Tetralogy of Fallot or similar lesions with decreased pulmonary blood flow related to reduced systemic vascular resistance and worsening right to left shunting, with or without acute pulmonary disease.

Immunosuppressed patients expected to have more severe disease include those CHD patients with underlying Trisomy 21, 22q11 deletion with thymic aplasia/hypoplasia, as well as heterotaxy patients who in addition to complex congenital cardiac lesions may have anatomical or functional asplenia.

Adolescent and in particular adult patients with untreated as well as palliated CHD have increased vulnerability and reduced functional reserve. These include Eisenmenger syndrome and patients post univentricular palliation and atrial switch procedures. Pregnancy represents a particularly vulnerable period for these women and there is a concern that difficulty in accessing healthcare could result in poor maternal outcomes.[41,42]

In the face of the pandemic, the greatest threat to child health is likely from the disruption of current healthcare systems.[43] Disruption already seen within the paediatric cardiac services includes:

- Postponement of elective clinic visits, surgery and cardiac catheterisations to reduce hospital and clinic volumes.
- Reduced access to healthcare services: Poor availability and increased cost of transport coupled with reduced household incomes, as well as confusion regarding safety and legality of movement has increased the number of patients missing essential visits and filling of their prescriptions. Limited internet and cell phone access reduces the utility of remotely filling prescriptions and "teleconsultations". CHD patients are at increased risk of severe disease from vaccine-preventable disease outbreaks due to reduced immunisations.
- The reluctance of patients requiring urgent interventions to be admitted for fear of contracting COVID-19 infection in hospital, has been exacerbated by reduced bed availability for boarder mothers in some hospitals as well as the prohibition or severe restriction of visitors in most institutions.

Should the pandemic progress as anticipated and services be overwhelmed or strained, surgical and catheter interventional services are likely to be further reduced or suspended. This will compound the existing burden of undetected and untreated CHD contributing to the significant mortality and morbidity of these patients.[44]

Rheumatic Heart Disease (RHD) is thought to affect at least 39 million people worldwide with the majority of these being young people, living in low- and middle-income countries and disproportionally affected by poverty, vulnerable health systems and poor access to tertiary medical and surgical interventions.[45] It is therefore most likely that patients with RHD will experience challenges during this period, both directly and

indirectly. The need for ongoing medical care, as with all chronic conditions, is particularly relevant to this population as a crucial part of prevention is regular monthly secondary prophylaxis.[46] Accessing this may be difficult or even impossible during this time. For those requiring ongoing medical treatment or therapeutic management of e.g. INR for those on warfarin, missing an appointment or blood test may result in life-threatening complications. The inability to access reproductive healthcare and contraception during this period can be associated with severe outcomes in women with prosthetic valves or mitral stenosis, as raised in the REMEDY study.[47]

CARDIAC CATHETERISATION AND INTERVENTIONS

Pediatric cardiology units are challenged for case selection during the COVID-19 pandemic. This can be ascribed to the paucity of guidelines, apparent lower impact of the virus in the pediatric population, limited scientific data and the unprecedented strain on hospital resources as a result of the coronavirus crisis.[48] Therefore, congenital cardiac programmes should be equipped to face a number of unique and fluid scenarios to deal with patients as the situation enfolds.

Although no definite recommendations exist for paediatric CHD patients, certain common themes are apparent in current literature and should be considered in congenital cardiac programmes during the pandemic.[49-53]

Protection of resources

Given the limited supplies of personal protective equipment (PPE), testing capability and ventilators, it is recommended to limit or postpone elective cases in order to make more of these valuable medical resources available for those in need. Local disease burden and changing patterns of disease put emphasis on the need for serial re-evaluation and situational analysis with appropriate adaptation of strategy. A proposed strategy for case selection is presented in Table 1. It should be recognised that each situation is unique, and management should be individualised; categorisation is no substitute for sound clinical judgment. It is also advisable that decisions should be discussed and coordinated with the local COVID-19 task team and/or departmental ethics committee.

Limiting exposure

In order to protect patients and catheterisation laboratory staff, exposure risks should be minimised. Compliance with social distancing and general infection control measures should be strictly adhered to. Algorithms should be developed and clearly communicated. Screening of patients is advised, but strategy should be determined by local resources and availability of adequate viral testing supplies. In a United States survey of congenital heart centres, Morray, et al. found that 65% of centres only screened for COVID-19 prior to cardiac catheterisation in the presence of symptoms of a viral prodrome; in this study merely 15% of centres screened all their patients.[52] It thus seems reasonable to make meticulous use of the COVID screening tool for all patients when cardiac catheterisation is indicated.

Use of PPE is vital to protect healthcare workers. Excellent resources are available to guide physicians in the management of patients with COVID-19 as well as donning and doffing of PPE.[50] These should be readily available and areas for donning and doffing should be clearly demarcated. It is advisable to do "test runs" and training to familiarise echocardiography and catheterisation laboratory personnel with patient management and correct donning and doffing techniques.

Limiting the number of staff (including trainees) in the cardiac catheterisation laboratory to the minimum is a logical precaution. This is even more important during aerosol generating procedures such as airway manipulation – ideally, a separate anaesthesia team should be dealing with this. Due to the limited number of healthcare professionals able to deal with congenital

TABLE I: Approach to cardiac catheterisation case selection.

Category	Urgent	Intermediate	Elective
Time frame*	Urgent	1 - 2 months	>3 months
Indicators	Impending haemodynamic compromise if not treated	Symptomatic or asymptomatic, but undue delay could be detrimental	Waiting period will not lead to undue harm
Examples#	Septostomy for TGV, PDA/RVOT stenting for decreased pulmonary blood flow, critical valvar lesions, etc.	PDA with heart failure, etc.	ASD device closure, PDA where heart failure can be controlled, pre Fontan evaluation, etc.

**Time frame – period for action; this must be individualised and based on clinical judgement.*
#Note that examples are not absolute or limited to those given. Clinical judgment/patient safety should always take preference.
TGV = transposition of the great vessels, PDA = patent ductus arteriosus, RVOT = right ventricular outflow tract , ASD = atrial septal defect.

cardiac disease, consideration should be given to splitting staff into 2 or more groups with the aim of ensuring at least 1 unexposed group in the event of COVID-19 exposure, in order to safeguard continuation of service.

Proper decontamination of the catheterisation laboratory after use is essential. Attention should be paid to the air-conditioning system and preferably a negative pressure room with the correct frequency of air changes should be used.

In the end, each congenital cardiac unit should decide how to best serve their community based on local/regional disease prevalence and availability of medical resources. By adhering to the principles described above, risks may be reduced for patients and staff.

CONCLUDING REMARKS

The COVID-19 pandemic represents the most important public health crisis of our lifetime. Moreover, its socioeconomic impacts, especially in the low to middle income countries like South Africa will be felt for many years to come. In South Africa, access to paediatric cardiac services is a challenge for the majority of our patients. This is due to a number of socio-economic and geographical reasons previously described by Hoosen et al.[44] The majority of paediatric cardiology services are offered in big academic hospitals catering for adults as well. As the pandemic surges, hospitals may prioritise the treatment for critically ill adult COVID patients, thus posing an ethical dilemma for the children with urgent and worsening CHD needing intervention.[54]

Mortality due to COVID-19 in children is reportedly low, with only few reported deaths. However, it would be prudent to assume that those with severe CHD are at higher risk of having severe COVID-19. Notably, the British Congenital Cardiac Association (BCCA) issued a statement to identify people with congenital heart disease who are at particularly high risk of becoming seriously ill from COVID-19 coronavirus.[55] The list included those patients with complex congenital heart disease (such as single ventricular physiology), patients with severe pulmonary hypertension, chronic cyanosis, unrepaired congenital cardiac lesion, and those with associated immunosuppression (e.g. such as trisomy 21, 22q deletion). It is important to ensure that patients continue to take the prescribed cardiovascular medications as the studies published have not shown any interference of this virus with these drugs.[54] As caregivers, we need to provide guidance to patients, parents and community, as well as those referring patients to our services (Table II). Global Arch together with Children's Heart Link has also issued the following guidelines: http://www.global-arch.org/covid-19-what-you-need-to-know/.

Appropriate management of this pandemic requires a careful coordinated approach involving various stakeholders who are all equally important. It is imperative that the Department of Health (DOH), National Institute for Communicable Diseases (NICD), cardiovascular societies or associations and local hospitals, should join forces in order to navigate this precarious period. During the pandemic, risk of transmission from patient to healthcare worker, healthcare worker to patient and healthcare worker to healthcare worker poses a major challenge. All referrals should be screened even at the time of discussion with referring colleagues prior to transportation. Therefore,

TABLE II: Advice and key messages.

General community	General practitioners and referring paediatricians	Patients and parents
All children should receive their routine vaccinations during this time. All children should be protected, and good food, exercise and regular activity should be encouraged. Children should not be separated from their parents if at all possible, with special emphasis on the breastfeeding infant. We support the role of schools (and the workplace) beyond just education: activity, social interaction but also food provision and protection from household violence. However, in the case of high-risk cardiac patients, the benefit of return to school should be carefully balanced against the risk of severe infection.	Cardiology services are still open albeit curtailed – speak to your local cardiologist if concerned Shortness of breath in children must be considered as a cardiac symptom, not only of COVID-19. Consider vaccination against the influenza virus and Palivizumab for the respiratory syncytial virus in infants, if available Discuss COVID-19 status of patient PRIOR to referral to a tertiary centre	We stress the importance of continuing with current medication. Contact your cardiologist if you are have an upcoming appointment – some of these appointments can be done remotely. Contact your cardiologist prior to coming to hospital if possible. Each hospital has new protocols regarding admission and screening upon arrival. High-risk cardiac children (complex defects, single ventricle), severe cyanosis, reduced cardiac function or heart failure, arrhythmias, pulmonary hypertension, heart surgery within the last 3 months or heart transplant patients should continue to be seen regularly.

universal precautions with frequent handwashing, social distancing measures, proper and appropriate use of PPE, and cleaning and disinfecting commonly touched surfaces, should be practised at all times.

EDUCATION AND FUTURE DIRECTIONS

In every crisis there is an opportunity to learn new things and explore novel ideas. Telemedicine has to be employed for patients' consultations and clinical case conferences with colleagues. It is imperative that service providers work together to ensure data are gathered on the number of patients tested, those diagnosed with the infection, and their outcomes. As we continue to learn more about the epidemiology, clinical manifestations and treatment protocols for COVID-19 in children, we should be responsive to new information, as this now emerges almost daily. However, data may be published in the lay press prior to peer-review or scientific substantiation, and care should be taken in this regard. We should use this opportunity to establish national registries and explore and support clinical trials, so that children, often forgotten, can also benefit from any emerging therapeutics or technologies.

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