Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Rethinking COVID-19 in children: Lessons learned from pediatric viral and inflammatory cardiovascular diseases

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In late 2019, a new virus, SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus strain 2), was reported in Wuhan, China [1]. The resulting COVID-19 disease has become a global pandemic, with 4.5 million cases reported worldwide as of May 16, 2020, which without universal COVID-19 viral testing almost certainly represents the tip of the iceberg [2]. When assessing SARS-CoV-2 infection, clinicians initially focused on symptoms in adults; however, emerging anecdotes, pre-prints, letters, and peer-reviewed reports suggest that children are also affected. Parents and clinicians have watched how, despite the incredible toll of COVID-19 on adults, the new coronavirus generally seemed to spare children [3,4]. As the outbreak spread to the US, data from Chinese health officials showed that children did not become infected in the same numbers as adults [5]. Diagnostic and therapeutic guidelines used for children are commonly extrapolated from studies conducted in adults. However, there are potential dangers in assuming that children are small adults and will have the same clinical presentation, course, and response to disease or therapy as adults, given many important physiological differences.

1. COVID-19 epidemiology

Children are a small fraction of confirmed COVID-19 cases—in China, Italy, and the United States, less than 2% of reported infections have been in children and adolescents less than 18 years old [6]. Researchers agree, however, that children with COVID-19 tend to respond better than adults do. Initial data suggested that children can transmit the virus but were far less likely to experience coronavirus-related complications [7].

Emerging evidence in the UK and US confirms that, although severe illness is less frequent in children, COVID-19 can have a marked disease burden in children and that existing comorbidities appear to be important in determining which children become infected [8]. Additional cases of children presenting with severe inflammatory syndrome with cardiovascular symptoms, and a laboratory-confirmed case of COVID-19 and an epidemiological link to a COVID-19 case have been reported [9].

Cardiovascular diseases in children related to viral illnesses and their therapies have been a focus of our research for decades and have resulted in several lessons that may be relevant to understanding the cardiovascular manifestations of COVID-19 in children. We need to determine the course, risk factors, and biomarkers that can predict outcomes for these children [10]. Some cardiovascular manifestations may be the result of direct viral infection of cardiomyocytes [11], but indirect effects from inflammation, coinfections, existing medical conditions, therapies, and genetic predispositions must also be considered [12–19].

Recently, 8 cases, including 1 death, have been reported in the UK [20]. In the 8 children, 6 were of Afro-Caribbean descent and 5 were boys. Antibody testing established that all 8 were positive for SARS-CoV-2. Notably, respiratory symptoms were not present in all cases. In Bergamo province, Italy, 10 cases of a Kawasaki-like disease were identified during the SARS-CoV-2 epidemic; this was a monthly incidence of at least 30 times greater than the average of 3 per month over the previous 5 years, an increase that clearly began after the first case of COVID-19 was diagnosed in the Bergamo area [21]. The researchers suggested that one of the coronaviruses might trigger Kawasaki disease because SARS-CoV-2 is a particularly virulent strain that can elicit a powerful immune response in the host. Among 48 children from 46 pediatric intensive care units in North America, in the US (none in Canada) enrolled in a 2-week study, 40 (83%) had preexisting underlying medical conditions, 35 (73%) presented with respiratory symptoms, and 18 (38%) required invasive ventilation. Hospital mortality was 4.2% (2 of 48) [22].

In a March 2020 study of households with confirmed COVID-19 cases in Shenzhen, China, [23] children younger than 10 years were just as likely as adults to become infected but were much less likely to

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have severe symptoms. However, other media reports, including some from South Korea, Italy, and Iceland, where testing has been more widespread, mentioned lower infection rates among children than among adults. Some Chinese studies also support the possibility that children are less susceptible to infection. One analyzed data from contact tracing in the Province of Hunan, China [24]. For every infected child under the age of 15 years, almost 3 adults between the ages of 20 and 64 were infected (odds ratio, 0.34; 95% CI, 0.24 to 0.49). A preliminary analysis of 300 infected children found that they produced much lower concentrations of cytokines than did infected adults. Cytokines are proteins released by the immune system; a fact consistent with Kawasaki disease as a condition associated with acquired immune dysfunction. Cytokines depress heart function through direct immune activation which can be associated with myocytolysis.

Increasing evidence suggests that bodily tissue damage in COVID-19 is mostly mediated by the host's innate immunity [25,26]. The disease is characterized by a cytokine storm resembling that of macrophage activation seen in viral-induced hemophagocytic lymphohistiocytosis [27]. In 2020, 102 children in New York State have had virus-related heart symptoms similar to those of Kawasaki disease and a toxic-shock-like syndrome, and 3 have died [28]. This new condition associated with COVID-19 has been named Pediatric Multi-System Inflammatory Syndrome (MIS-C), whose primary symptoms consist of persistent fever, extreme systemic inflammation, and evidence that one or more organs are not functioning properly, but the mechanisms of the syndrome remain unclear.

Laboratory evidence of inflammation includes, but is not limited to, one or more of the following: an elevated erythrocyte sedimentation rate and elevated concentrations of C-reactive protein, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin 1 and 6, or neutrophils and lower concentrations of lymphocytes and albumin. Notably, these cases begin to appear about a month after related adults become symptomatic for COVID-19 [29].

Some symptoms can resemble those of Kawasaki Disease Shock Syndrome [30]. Kawasaki disease [31] is an acute and usually self-limiting vasculitis of the medium-caliber vessels, which almost exclusively affects children. In serious cases, COVID-19 can cause heart swelling and damage; fever with many symptoms, including rash; conjunctivitis; redness in the lips, tongue, and mucous membranes of the mouth and throat; swollen hands or feet; and sometimes enlarged lymph nodes on one side of the neck. In some children with COVID-19 disease, enlarged coronary arteries and aneurysms may contribute to blood clots [32]. Some children have had coronary artery aneurysms. The number of similar cases—including several deaths—has been increasing in other parts of Europe, although the cause of these aneurysms is not well-understood [33]. Reports also commonly describe elevated serum biomarker concentrations for inflammation [34]. Cytokines depress heart function through direct immune activation that can be associated with myocytolysis. Most children have responded to high doses of aspirin, intravenous immunoglobulin, steroids, and cytokine blockers [35]. Evidence from Europe suggests most children will recover with evidence-based critical and supportive care, some requiring VA-ECMO, as with one 14-year-old boy in London who died [20].

2. Myocardial damage

Clinical myocarditis is uncommon in infants and children, but most cases in children are caused by a viral infection. The most common pathogens are Coxsackievirus B [36], but other enteroviruses [37], influenza [38], rubella [39], adenoviruses, and a host of other agents have also been implicated. The offending agents trigger an immune response, resulting in myocardial edema that eventually impairs systolic and diastolic ventricular function. Although Coxsackie B disease is not usually fatal, the reoccurrence rate is 20%, and heart damage is typically permanent [40]. Newborns and infants are more severely affected because the immature myocardium is less able to adapt to an acute insult.

The cardiovascular findings in COVID-19 are similar to those of Kawasaki disease, [41–43] a well characterized cardiovascular condition in children. Kawasaki disease is sometimes proposed as a model for all pediatric viral cardiovascular diseases by generalizing its course, risk factors, validated surrogate markers of outcome, and therapies are generalized to other viral cardiovascular diseases. We have not found this model useful in other pediatric viral cardiovascular diseases, as detailed below [44]. Moreover, No single risk factor for Kawasaki Disease explains more than a small percentage of the overall risk of contracting the disease.

Children may present with sinus tachycardia and a gallop on auscultation, cardiomegaly on radiographs, and small voltages on electrocardiograms [45]. Several studies have reported that myocarditis can affect cardiac function for life [46–48]. One study found that 2 (9%) of 21 children with presumed to have viral-induced myocarditis had dead and dying heart muscle similar to that found after an acute infarction that responded to repeated, high doses of intravenous immunoglobulin [49]. Nonspecific biomarkers of inflammation (white blood cell count, C-reactive protein, and erythrocyte sedimentation rate) are often elevated in viral myocarditis [50]. Elevated blood concentrations of cardiac troponins T and I are markers of cardiomyocyte damage or death and have been reported in substantial numbers of children with myocarditis [51–53]. When symptoms repeated over several clinical episodes, many children show a “burned out” myocardium with end-stage dilated cardiomyopathy [54]; nevertheless, myocarditis can have an ominous prognosis in newborns. Mortality when Coxsackievirus B is the suspected pathogen can be as high as 75% [55]. Mortality is less than 25% in older children, and another 25% will have chronic symptoms of heart failure. Recovery is complete in half of children with myocarditis [56].

Sudden death in children is commonly associated with myocarditis. Sudden death occurred in 57% of autopsied patients with a diagnosis of myocarditis at a single pediatric center in children over 12 years with a median age of 10 months (range, 10 days to 16 years) [57]. Studies of sudden infant death syndrome have linked infection with viruses such as enterovirus, adenovirus, parvovirus B19, Epstein-Barr virus, and to myocarditis [58,59].

3. Treatment

First-line treatments COVID-19 myocarditis include rest, oxygen, and diuretics. Inotropic agents are useful for treating moderate-to-severe heart failure. Most children have responded to anti-viral agents [60,61], intravenous immunoglobulin, steroids, and cytokine blockers [47]. Registry studies show improvements in systolic ventricular performance in viral heart diseases treated with cause-specific antiviral therapy [62]. We found that monthly immunomodulatory treatment with IVIG markedly improved cardiovascular structure and function in these virus-infected children [63]. Further, we have found that some of these infected children have progressive cardiovascular abnormalities that are strongly associated with chronic inflammation [64]. Acute and chronic immune activation also affects vasculitis in these children [65,66].

However, from longitudinal follow-ups of other virus-exposed or infected children, we have learned that viral-associated cardiovascular diseases in children are much more complicated than indicated by the mere assessment of systolic ventricular performance [67]. Assessing the global risk of developing symptomatic cardiovascular disease by using pathobiological determinants of atherosclerosis in youth coronary arteries and abdominal aorta risk scores calculated by measuring a combination of modifiable risk factors, along with other surrogate markers of symptomatic cardiovascular disease, are more informative than assessing systolic ventricular performance alone [67]. For example, although antiviral therapy increases LV systolic performance in

virus-exposed or infected children, it can also result in long-term diastolic dysfunction [68], as well as other major persistent or progressive cardiovascular issues. One of the remarkable outcomes is that these hearts often remain too small for the body as these children grow, perhaps because of the stunting effects of viral replication leading to stunting of cardiac growth [69,70], which may eventually be associated with premature symptomatic cardiovascular diseases.

Children with myocarditis who have a swollen endothelium and depressed heart function are particularly vulnerable to cardiotoxic medications, such as hydroxychloroquine alone or in combination with azithromycin [71]. This vulnerability is secondary to genetic susceptibility and variability and is associated with mitochondria mutations [72]. Antiviral therapy-associated cardiotoxicity in these children is not a class effect. Rather, specific antiviral therapies can have more deleterious effects on cardiovascular structure and function [73], allowing antiviral therapy to be tailored to achieve the greatest efficacy while minimizing cardiovascular toxicity. Chloroquine and its drug derivatives can be particularly toxic to children's hearts, by affecting the intracellular pH, which can result in electrolyte abnormalities, cardiotoxicity, and prolonged QT intervals. Several over-the-counter medications have been removed from the market, because they can increase the risk of QT-prolongation, which is associated with sudden death in children with myocarditis and other heart damage [74]. For example, the US FDA issued a “Black Box” warning that long-acting stimulant therapy for children with underlying cardiovascular disease should be carefully assessed, given a possible association with sudden death [75,76].

4. The importance of patient registries

Multicenter, pediatric cardiovascular disease registries comprised of prospectively collected data have supported treatments that have reduced the failure of medical management of cardiomyopathy by 50% at participating centers [77], emphasizing the importance of registry-based research that may lend itself to COVID-19 cardiovascular diseases. With data from a registry, we recently developed a new classification system for pediatric myocardial diseases [78] by identifying differences in the course and outcomes specific to the causes of several cardiomyopathies [79]. Competing-risk analyses established that children with suspected myocarditis have outcomes similar to those in children with histologically proven myocarditis, a finding that can avoid the risks of biopsy. Although echocardiograms of children with myocarditis may be similar to those with dilated cardiomyopathy, their course and outcomes differ, which may help manage COVID-19 cardiac disease [54].

A final note here about the need to ensure the safety of the providers caring for children with COVID-19. In the current COVID-19 pandemic there is significant concern among all clinicians around the potential consequences of being infected, including history of immune suppression, diabetes, heart disease, and also seems to have an increased effect in the Black, Asian and Minority Ethnic (BAME) community due to the excess deaths faced by this cohort [80,81]. Several groups around the world are recommending to risk stratify healthcare workers as a way to best protect healthcare workers that are most at risk of getting infected [82]. Related, the coronavirus pandemic has greatly affected how echocardiograms are acquired in the intensive care unit and perioperative settings. Careful consideration of the indications, venues, and approaches for echocardiographic imaging will protect healthcare providers, and preserve the operational integrity of health systems [83]. Echocardiography personnel can be further protected by carefully reassigning those at increased risk for infection, such as advanced age, chronic conditions, immunosuppression, and pregnancy [84].

5. The need for immunology research strategies

COVID-19-associated cardiovascular disease is thought to be associated with both immune activation and viral effects in some affected children. This immune vulnerability makes it imperative to determine whether this Kawasaki disease-like illness is causally associated with COVID-19 and, if so, to identify the biological and immunological processes involved. While generally self-limited, Kawasaki Disease can have a number of long-term sequelae, the most important of which are cardiovascular.

Tomisaku Kawasaki first reported his 50 cases in Japan a half-century ago, but the definitive causes of Kawasaki disease remain unknown [31]. Serum cardiac troponin concentrations are consistent with active cardiomyocyte injury that goes beyond the often-reversible myocardial depressant effects of certain cytokines that are activated or that “storm” in some of these children. These conditions suggest that children are likely to experience long-term cardiovascular effects because cardiomyocyte death or mitochondrial damage are often irreversible.

Some investigators have suggested that the coronavirus family might be one of the triggers of Kawasaki disease, SARS-CoV-2 being a particularly virulent strain able to elicit a powerful immune response in the host [85]. Intriguing questions have been raised about the affinity of the coronavirus and the Angiotensin Converting Enzyme 2 (ACE2) receptor for cell entry, which is also associated with Kawasaki disease [86]. A recent study examined upper and lower airway cells for the expression of *ACE2*, the gene that codes for the receptor that the coronavirus uses to infect cells [87]. Preliminary evidence suggests that an allergy paradoxically may reduce the susceptibility to SARS-CoV-2 infection and severe COVID-19 disease. In both children and adults, respiratory allergy, asthma, and controlled allergen exposure were associated with greatly reduced *ACE2* expression. The expression of *ACE2* was lowest in people with more severe asthma and a higher sensitivity to allergens.

We have found that some children acutely treated for cancer can have a similar pattern of dead and dying cardiomyocytes and irreversible mitochondrial injury [88]. In these children, one of the leading mechanisms is free-radical injury to cardiomyocytes and their mitochondria from the cancer and its treatment. In high-risk children with a genetic predisposition [89] or exposure to certain risk factors and cancer therapies, treatment that reduces free-radical injury results in substantially fewer damaged cardiomyocytes and mitochondria with less cardiac injury even years later [90–93]. These results indicate the need to understand the course, risk factors, and biomarkers of pediatric cardiovascular covid-related diseases to support the development of cause-specific therapies and to prevent toxicity and late effects. Many lessons are to be learned, but targeted discovery is key. We have suggested a research agenda and funding strategies that may lead to better clinical outcomes for children at risk of cardiovascular diseases [94–96].

6. Clinical testing

Children are currently not tested for COVID-19 as often as adults are because they have no or only mild symptoms. We need to know whether the rates of SARS-CoV-2 infection differ between children who have asthma or other allergic conditions and children who do not [97].

For children with presumed acute-onset viral disease, detecting active myocardial involvement is critical because its symptoms can be wrongly attributed to respiratory or infectious complications, delaying appropriate therapy [98,99]. We found that nearly 10% of children presenting to the emergency department of a major children's hospital with presumptive viral febrile illnesses had active myocardial injury, characterized with dead and dying cardiomyocytes, and about 2% had serum concentrations of cardiac troponin T similar to those found in adults with acute myocardial infarctions. Yet for these young children, cardiac involvement was clinically unsuspected [100]. “If you don't look for it, you may not find it.” Further, some of these cardiac biomarkers are validated predictors of long-term cardiovascular health or disease in children, which better informs treatment decisions in high-

risk groups [101]. The possibility of unsuspected myocardial injury suggests that children with symptoms of COVID-19 infection should also be screened for cardiac involvement by measuring serum concentrations of cardiac troponin and NT-proBNP, both of which have low costs in time and money and would not delay potentially more appropriate therapy.

7. Conclusions and recommendations

We believe the growing threat to children from COVID-19 supports the following recommendations for policymakers and clinicians.

1. Organizational learning must be a top priority

The COVID-19 pandemic has seriously tested the reliability of social, learning, and governance systems [102]. Peer to peer, "horizontal learning" that brings researchers, clinicians, and policy makers together to create a "community of practice" is an innovative and comprehensive approach to pediatric multidisciplinary "action research." The resulting learning collaboration can be a powerful tool to improve COVID-19 learning [103]. Multi-stakeholder collaborations and authentic learning partnerships can address the tempo of learning from the widespread care of all children with COVID-19 while reducing harmful and unscientific variations in COVID-19 cardiac care [104]. Evidence has shown that creating this "community of practice" builds trust, shares knowledge, and generates empirical evidence to use and disseminate innovative quality-improvement initiatives to improve communication, coordination, and clinical teamwork [105]. The approach represents a fundamental paradigm shift in that it actively seeks to bridge disciplinary silos and to address knowledge gaps within and across COVID-19 care delivery system [106]. Such an approach can support the creation of an integrated research and implementation continuum, stretching from prehospital care to long-term wellness that can transform the care delivery services and spread innovation and uptake [107].

a. Agree on Definitions and Data Collection. We need to obtain consensus on common diagnostic definitions and to ensure their widespread and consistent use by providers, public health officials, and policymakers [108,109].
b. Identify and Validate Surrogate Endpoints. Conducting trials in children with heart failure is challenging because selecting and interpreting study endpoints to evaluate policy and service interventions remain contested [110]. Many studies of these children have tested the utility of serum biomarkers, imaging studies, and disease severity as surrogate endpoints. Although such endpoints have been proven useful for risk stratification, none have been validated as predictors of "hard" clinical endpoints in this population [111,112].

c. Fund and Support Cardiac Registries. A global pediatric COVID-19 cardiac registry of patient characteristics and outcomes [113], modeled, for example, after the Pediatric Cardiomyopathy Registry, should be established as soon as possible. Similar pediatric registries have proven their value in understanding and treating diseases in children [114].

2. Health Policy Funding Priorities. Funding needs to be increased substantially for pediatric public health; test development, supplies, and personal protective equipment; and for the routine application of serological testing, once available and well-validated, in the diagnosis and management of COVID-19 patients. At the same time, targeted funding for COVID-19 pediatric cardiac injury research is needed to support longitudinal studies of immune response and risk of re-infection [115,116].

3. Better Child Screening. Large, high-quality population studies are needed. Symptomatic children should be tested for COVID-19 infection and for serum concentrations of cardiac troponin and NT-proBNP to screen for occult cardiac involvement.

4. Protecting Health Care Workers. The safety and wellness of healthcare workers must be ensured. Data from China [117], Italy, Spain, Italy, UK [118], Mexico, and the US show that tens of thousands of responding health-care workers have been infected and hundreds have died [119]. In the UK and the US, most healthcare workers who have died have come from black, Hispanic and Asian backgrounds [81]. Reports from medical staff describe physical and mental exhaustion, the torment of difficult triage decisions, and the pain of losing patients and colleagues, all in addition to the ever-present risk of potentially fatal infection. Assuring adequate availability of personal protective equipment is just the first step; other measures must be considered, including cancelling non-essential medical care and group events to concentrate resources and providing food, rest, and personal and family psychological support [120]. In any pandemic, health-care workers are every country's most valuable resource.

5. Virtual Care is the Future. The movement toward virtual visits aims to protect children, their families, and healthcare workers from exposure to COVID-19, so eliminating as much in-person traffic and contact as possible at hospital and clinics is essential. Telemedicine is not new, but the urgency of the COVID-19 crisis has forced most healthcare organizations to make radical shifts to telehealth within a few weeks, transitioning most appointments to a telemedicine platform. Using appropriate software, clinicians can carefully triage upcoming appointments to select children most appropriate for telemedicine visits and those who should be seen in person, such as patients who need to come in for chemotherapy infusions. We need to better understand how and when to best use patient-facing digital health technologies and how these technologies influence the quality, safety, and satisfaction of children and their families [121].

6. Inequity. Pediatricians, health service researchers, and policy makers are not at all surprised to read headlines about the disproportionately high numbers of COVID-19 deaths among the poor, underrepresented minorities (black and minority ethnic backgrounds) and people who are in nursing homes, marginalized and homeless, incarcerated, highly religious, and indigenous. Unfortunately, the number of minority healthcare providers and social workers that have been infected and died is also disproportionally high [81]. It is time to commit the resources and political will to address inequalities in care, especially among children.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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