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.

Trends in Cardiovascular Medicine 30 (2020) 397–398

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Editoral commentary: Cardiac involvement in SARS-CoV-2-associated inflammatory syndromes ☆

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ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Multisystem Inflammatory Syndrome in Children (MIS-C)
Kawasaki Disease
Inflammation
Cardiovascular System
Adult Respiratory Distress Syndrome (ARDS)
Extracorporeal Membrane Oxygenation (ECMO)

In their review discussing the effects of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in children and adolescents, Loke, Berul and Harahsheh highlight the overlapping features between Kawasaki disease (KD) and the recently described inflammatory syndrome called Multisystem Inflammatory Syndrome in Children (MIS-C) [1].

Regrettably, Dr. Kawasaki, who initially described the disease that bears his name, passed away last month. He started studying this unreported sickness in 1961, labelling the relevant folder "G.O.K" for "God Only Knows" [2]. Since then, numerous novel infectious and inflammatory diseases have appeared, but the world has rarely seen a large-scale infectious disaster like coronavirus disease-19 (COVID-19). First reported in China in December 2019, COVID-19 initially appeared among workers at a food market in Wuhan, presumably secondary to viral transmission from bats [3]. The World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern on January 30th, 2020 and released interim guidelines for patient management [4]. However, due to the infection's rapid and devasting spread worldwide, that same organization declared COVID-19 a pandemic on March 11th[5].

It initially seemed that this new disease only affected seniors, especially those with pre-existing comorbidities like diabetes and obesity. Soon, however, it increasingly became evident that COVID-19 also could affect middle-aged and, albeit less frequently, young adults. It also initially seemed that only the lungs were involved, with involvement similar to adult respiratory distress syndrome (ARDS); but this too was discovered to be inaccurate. Pulmonary involvement was only one aspect of COVID-19, true nature of which was that of a systemic, inflammatory disease that could involve other organs, including the cardiovascular system, in many ways [6].

Finally, even children and adolescents, heretofore believed to be immune to COVID-19's effects, were getting sick, albeit in a way different than adults. This was first observed in the United Kingdom [7] where critically ill children with overlapping features of atypical KD and toxic shock syndrome were found to test positive for SARS-CoV-2. This new condition was soon recognized by both the Centers for Disease Control (CDC) in the United States [8], and WHO [9], who characterized the condition differently. The CDC characterization, named *Multisystem Inflammatory Syndrome in Children (MIS-C)* with COVID-19, has been more uniformly adopted. Clinical features of MIS-C are fever, multi-organ dysfunction, evidence of inflammation with high neutrophilia and elevated inflammatory markers, and exclusion of any other microbial cause [1].

For their review, Loke et al compiled data on 130 children across five countries (Italy, France, Switzerland, USA, UK) whose ages ranged from 1.8—16 years. All had fever. Other common symptoms/signs included abdominal and respiratory symptoms (in 70 and 40%, respectively), skin rash (55%), conjunctivitis (61%), and fissured lips or strawberry tongue (41%) [1]. The review highlights the cardiac and other features that overlap MIS-C and KD. One peculiar aspect of KD is coronary aneurysm formation, which is identified in roughly 25% of untreated patients. Aneurysm formation

☆ **Declaration of Competing Interest:** None

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https://doi.org/10.1016/j.tcm.2020.07.008

may be followed by thrombosis, myocardial ischemia, and even cardiac death. Myocarditis also may occur. Often, there is left ventricular dysfunction and hypotension, and sometimes, cardiogenic shock. In MIS-C, aneurysm formation has been observed in 15% of patients, including two with giant coronary aneurysms, as has circulatory shock requiring fluids or vasoactive drugs in 64% of cases, arrhythmias in 6%, and decreased left ventricular function in 56% [1].

In adults affected by COVID-19, the incidence of acute cardiac injury varies from 7—28% among hospitalized patients, but this number is partially dependent upon the definition of "cardiac injury" used [10–12]. In the literature, this varies from cardiac troponin elevation ≥99 percentile alone, to troponin elevation plus a composite of echocardiographic and electrocardiographic abnormalities. Ventricular tachycardia and fibrillation have been seen in 6—44% of patients. Heart failure, cardiogenic shock and myocarditis have also been described. While myocarditis is quite infrequent, heart failure has been a reported complication of COVID-19 in 23% [11]. Furthermore, coagulation and fibrinolytic system dysfunction — characterized by prolonged prothrombin times, elevated D-Dimer levels and activated partial thromboplastine time, disseminated intravascular thrombosis, venous and arterial thrombi, and pulmonary emboli — has become a prominent feature in adults [13]. Mechanisms of cardiac injury vary from inflammation to toxicity from direct viral injury, oxygen supply-to-demand mismatch, microvascular dysfunction, and plaque rupture. Also in adults with COVID-19, the systemic inflammatory response — characterized by elevated inflammatory biomarkers, cytokines (e.g., interleukin-2R, tumor necrosis factor, interleukin-6), C-reactive protein, and ferritin — may be devastating, even leading to a cytokine storm and multi-organ dysfunction [14].

Although in children with MIS-C, the inflammatory response may sometimes be associated with transitory respiratory impairment, this feature is more prominent in adults with COVID-19, who may even require venous-venous extracorporeal membrane oxygenation (V-V ECMO) support. WHO guidelines recommended administering V-V ECMO to eligible patients with COVID-19-related ARDS at centers with sufficient case volumes and extensive clinical expertise [4,5]. However, notwithstanding the existence of considerable observational data on the use of ECMO for influenza A (H1N1) and Middle East Respiratory Syndrome (MERS) coronavirus-related ARDS, the real utility of ECMO in adult COVID-19 patients with respiratory failure is uncertain and remains under investigation [15]. To date, data in adults suggest that roughly one out of every 2-3 patients on V-V ECMO survive [16], while outcomes with A-V ECMO for MIS-C-related cardio-circulatory impairment are almost always favorable [1]. While Europe carefully reopened its borders to travelers after the incidence of new COVID-19 cases dramatically decreased during a lockdown, the virus continues to run rampant in the United States and Latin America. There also is the possibility that a new outbreak will arise in Europe next autumn, which makes it crucial to further study the role of ECMO in COVID-19.

In conclusion, SARS-CoV-2 may generate an inflammatory syndrome in both adults and children, albeit with several different characteristics and consequences. Among them is that adults experience more aggressive respiratory involvement, while children exhibit more of a cardiac and systemic inflammatory syndrome with overlapping features of Kawasaki's disease. Loke et al. should be congratulated for examining the link between MIS-C and KD. Much research remains necessary to better understand the nature and optimize the treatment of MIS-C.

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