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REVIEW ARTICLE

Cardiac Involvement Related to COVID-19 Infection and Vaccination in Children and Adolescents − Hong Kong's Perspective

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Abstract

Myocarditis and Pericarditis have many virological and immunological causes. This article described the SARS-CoV involvement to the heart in children and adolescents, also the entity Multisystem Inflammatory Syndrome in Children (MIS-C), a rare but severe consequence of SARS-CoV2 infection. Hong Kong case definition of MIS-C was listed. The consensus from overseas experts was that MIS-C should be managed by multidisciplinary team with a structured long-term follow-up to monitor the functioning of various organs and ascertain the prognosis. The side effect mRNA vaccination causing myocarditis and pericarditis is also concern of paediatricians worldwide. Hong Kong published local epidemiology of acute myocarditis and pericarditis among adolescents following Comirnaty vaccination, the local and overseas data were used in fine-tuning the COVID vaccination program in children and adolescents. To prevent severe and fatal outcome of COVID-19 diseases, it is important to educate the public and to promote COVID-19 vaccination in the community, also to continue monitoring the safety of the available vaccines.

Keywords: COVID-19, SARS-CoV2, Multisystem inflammatory syndrome, mRNA vaccination, Myocarditis and pericarditis

Myocarditis/pericarditis have many virological and immunological causes [1,2], both can occur after SARS-CoV-2 infection alone or as a consequence of multisystem inflammatory syndrome in children (MIS-C) following COVID-19 infection [3,4].

COVID-19 infection can affect different organ systems, cardiovascular complications is one of the main concerns, in particular among children with pre-existing congenital heart diseases [5−7]. Injury to the myocardium can be resulted from a direct invasion of the virus or related to an exaggerated

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immune response [4,6,7]. Viral entry via angiotensin-converting enzyme-2 (ACE-2) receptor is considered to be the mechanism leading to damage of target cells including cardiomyocytes [8]. Other reasons causing the myocardial damage can be related to immune-mediated injury secondary to excessive cytokine release or T-cell dysregulation, microvascular damage, endothelial shedding/dysfunction, and hypoxia-mediated injury resulting from a thromboembolic phenomenon [9].

Multisystem inflammatory syndrome in children (MIS-C)

MIS-C, also termed Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS), is a severe multisystem inflammatory syndrome associated with COVID-19 infection. MIS-C typically presents 2−6 weeks after exposure to SARS-CoV-2 [10,11]. Patients can present with a wide range of symptoms and signs, such as persistent fever, polymorphic rashes, gastrointestinal symptoms, conjunctivitis, and mucosal changes [10−12]. There is also severe systemic inflammation as evidenced by the elevation of inflammatory markers (ESR, CRP, ferritin), multiple organ dysfunction, and cytokine storm (particularly raised IL-6 level) among these patients. Some children with MIS-C required intensive care because of hypotension due to acute myocardial failure, systemic hyperinflammation, and vasodilatation, requiring inotropic support [13,14]. Other significant cardiac manifestations, including coronary dilatation, aneurysms, and arrhythmias, have also been reported. Troponin level and N-terminal pro-B type natriuretic peptide (NT Pro-BNP) are useful markers of cardiac involvement and subsequent monitoring. Despite similarities in the clinical presentation of MIS-C and Kawasaki Disease (KD), infectious diseases experts considered them to be two rather different entities [15,16]. Children with MIS-C were generally older and had much higher levels of inflammatory markers than KD. Patients with KD were more likely to have rash (96.0% vs. 50.2%; $P < 0.001$), conjunctival injection (94.1% vs. 61.8%; $P < 0.001$), and coronary artery abnormalities (28.7% vs. 15.0%; $P = 0.006$) but less likely to have other cardiovascular outcomes (myocarditis, decreased cardiac function, mitral regurgitation, pericardial effusion), as well as gastrointestinal, neurologic, or renal involvement. Patients with MIS-C had elevated CRP and decreased platelet counts, and lymphocyte nadir counts compared with patients with COVID-19 and KD. Patients with MIS-C shock were more likely to report abdominal pain (77.0% vs. 27.3%; $P = 0.003$) and headache (49.2% vs. 0%; $P = 0.001$), whereas patients with KD shock syndrome (KDSS) were more likely to have coronary artery dilatation or aneurysm (63.6% vs. 17.7%; $P = 0.002$) and rash (90.9%−48.7%; $P = 0.009$). Patients with MIS-C shock had lower lymphocyte counts (median, 580/μL vs. 1350/μL) and shorter duration of fever (median, 5 vs. 7 days; $P = 0.020$) [16].

Given a growing number of complicated paediatric COVID-19 cases and the occurrence of MIS-C associated with COVID-19 infection in Hong Kong since mid-March 2022, expert group meetings with presentation from overseas expert and separate sharing of clinical experience among colleagues in different HA Paediatric Departments and private sector who have managed MIS-C cases in Hong Kong were hosted at the ChildSim, Simulation Training Centre of Hong Kong Children's Hospital in April 2022 [17−19]. The special presentation by various hospital representatives on April 27, 2022 not only facilitated a fruitful exchange of clinical knowledge and management but also enabled agreeable standardized local reporting criteria for MIS-C to be established through reviewing currently available evidence and different international diagnostic criteria (Table 1) [20−22]. It was suggested that post-infectious immune dysregulation, an aberrant development of acquired immunity to SARS-CoV2, is probably the reason causing MIS-C [14,15,23], but further research is needed to delineate the pathophysiology.

The treatment goals for MIS-C are to decrease the systemic inflammation, restore the organs' function, decrease the mortality and reduce the risk of long-term sequelae such as the neurological complications [24], development of coronary artery aneurysm, and cardiac dysfunction. However, the optimal therapeutic strategy is still uncertain as current studies still did not find evidence suggesting the outcomes recovered from MIS-C being differed after treatment with 1) intravenous immunoglobulin (IVIG) alone, 2) with IVIG plus glucocorticoids, or 3) with only glucocorticoids [25]. The consensus from overseas experts was that MIS-C should be managed by a multidisciplinary team with a structured long-term follow-up to monitor the functioning of various organs and ascertain the prognosis [24,26−28].

Post-COVID vaccine myocarditis

In Hong Kong, the COVID-19 vaccination program started on February 26, 2021. The available vaccines for public use include the CoronaVac (an inactivated virus vaccine developed by Sinovac) and the Comirnaty (BNT162b2 mRNA vaccine co-developed by BioNTech and Pfizer and manufactured and distributed in China by Fosun Pharma). The Food and

Table 1. Hong Kong case definition of multisystem inflammatory syndrome in children (MIS-C).

All six criteria need to be met:
1. Children and Adolescents from 0 to 17 years old.
2. Evidence of SARS-CoV-2 infection: documented [1] RAT + ve, or [2] PCR + ve, or [3] positive SARS-CoV2 Ab or [4] contact history with an individual with SARS-CoV-2 infection.
3. Fever for ≥24 hours.
4. Two or more organs involvement:
   - Gastrointestinal System: e.g. Vomiting, diarrhoea
   - Hepatitis, pancreatitis
   - Central Nervous System e.g. Change in conscious state, seizures, meningitis
   - Respiratory: e.g. Pneumonia, pleural effusion
   - Dermatological: e.g. Mucosal changes (conjunctivitis, red and cracked lips, strawberry tongue), erythematous skin rashes
   - Coagulopathy: e.g. Platelets and white blood cell abnormalities, deranged clotting profile, raised D-dimer level
   - Cardiovascular system: e.g. Pericarditis, myocarditis, coronary artery dilatation, shock
   - Renal system: e.g. acute kidney injury
5. Evidence of inflammation with elevation in any i nflammatory markers: ESR, CRP, CK, Troponin, Ferritin, NT-ProBNP
6. Infection or inflammation cannot be explained by other pathogens.

RAT, rapid antigen test; PCR, polymerase chain reaction; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CK, creatinine kinase; NT ProBNP, N-terminal pro-B type natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ab, antibody.

Health Bureau, Hong Kong SAR Government, lowered the age limit for receiving the Comirnaty vaccine to ≥12 years on June 14, 2021 [29]. Since April 2021, there have been reports that myocarditis and pericarditis have occurred in adolescents and young adults after mRNA COVID-19 vaccinations internationally [30−32], which is an uncommon association as it is known to be a rare association following smallpox vaccination (around 12−16.1 per million vaccinated individuals) [33].

Between June 14, 2021 and September 4, 2021, 33 cases of myocarditis and pericarditis following Comirnaty vaccination were identified using the criteria created by the Cardiovascular Injury-Coalition for Epidemic Preparedness Innovations (CEPI) and the Brighton Working Group [34]. Among these adolescents, 29 (87.88%) were male, and 4 (12.12%) were female, with a median age of 15.25 years. 27 (81.82%) and 6 (18.18%) cases developed acute myocarditis and pericarditis after receiving the second and first dose, respectively. All patients have a relatively mild course and required conservative management only. The overall incidence of acute myocarditis and pericarditis was 18.52 (95% confidence interval [CI], 11.67−29.01) per 100,000 persons vaccinated. The incidence after the first and second doses were 3.37 (95% CI, 1.12−9.51) and 21.22 (95% CI, 13.78−32.28) per 100,000 persons vaccinated, respectively. Among male adolescents, the incidence after the first and second doses were 5.57 (95% CI, 2.38−12.53) and 37.32 (95% CI, 26.98−51.25) per 100,000 persons vaccinated.

An increase in the incidence of myocarditis and pericarditis was found following the second dose of mRNA vaccine, especially among the young male adolescents, which concurred with the observation in other parts of the world [29,35]. Balancing the risk of myocarditis and the benefit of protecting against severe COVID-19 infection, adolescents aged 12−17 years old in Hong Kong were recommended by JSC-EAP (the Joint Scientific Committee on Vaccine Preventable Diseases (SCVPD) and the Scientific Committee on Emerging and Zoonotic Diseases (SCEZD) under the Centre for Health Protection of the Department of Health (DH) joined by the Chief Executive's expert advisory panel (EAP)) to receive only one dose of the BNT162B2 instead of two doses since September 15, 2021 [36]. A cohort study confirmed that the adopted single-dose regimen was associated with a significant reduction in the risk of developing myocarditis among adolescents in a setting with no evidence of local transmission [37]. Another mouse-model study also demonstrated that administering the BNT162b2 intravenously induced acute myocarditis, which has raised the attention of the JSC-EAP [38]. The JSC-EAP thus recommended that the option for intramuscular injection of the Comirnaty vaccine at the mid-anterolateral thigh should be considered, especially for children and adolescents [37]. A case-control study demonstrated the increased risk for carditis after using the mRNA BNT162b2 vaccine but not the inactivated COVID vaccine CoronaVac [39].

The pathophysiology of mRNA vaccine-induced myocarditis is yet to be unraveled. The autopsy report from a case from Korea who died from mRNA-vaccine-induced myocarditis demonstrated that it is histologically different from viral or immune-mediated myocarditis. The mRNA vaccine-induced myocarditis was predominantly characterized by neutrophil and histiocyte infiltrates, rather than lymphocytes. Furthermore, single-cell necrosis of myocytes without inflammation was at multiple sites throughout the atria and multiple contraction band necrosis predominantly in the left ventricle [40]. More studies will be needed to define the pathophysiology of mRNA vaccine-induced myocarditis.

At the beginning of the Omicron-variant outbreak in December 2021, emerging scientific data suggested that two doses of the Comirnaty vaccine administered at a longer interval greater than 8 weeks have a lower

risk of myocarditis and pericarditis when compared to receiving at a shorter interval and without compromising the immune responses [41]. On December 23, 2021, the JSC-EAP recommended that adolescents aged 12 to 17 receive two doses of the Comirnaty vaccine at least 12 weeks apart [42]. Between September 15, 2021 when JSC-EAP recommended one dose of mRNA vaccine and December 23, 2021 when JSC-EAP modified the recommendation back to 2 doses, there were only 6 reported cases of myocarditis (2 definite, 3 probable, and 1 possible) and 1 probable perimyocarditis. As Hong Kong faced the fifth wave of the COVID-19 outbreak due to the Omicron variant in February 2022, the JSC-EAP further recommended shortening the time interval between the two doses of receiving the Comirnaty vaccines from 12 weeks to 8 weeks for children and adolescents aged 5−17 years to provide adequate protection against COVID-19-related severe complications. Third dose mRNA BNT162b2 vaccine can also be considered for adolescents aged 12−17 years old at an interval of 5 months after the second dose. In addition, the JSC-EAP continued recommending intramuscular injection of the Comirnaty vaccine at the mid-anterolateral thigh, especially for male children and adolescents, to reduce the risk of vaccine-related myocarditis [43]. Since February 2022, there are 6 reported cases of adolescents (3 with myocarditis, 1 with perimyocarditis, and 2 with pericarditis) developing myocarditis and pericarditis after receiving the third dose mRNA BNT162b2 vaccine. In a recent population-based study conducted in the UK, it is also observed that there is also an increased risk of myocarditis following sequential doses of the BNT162b2 vaccine, including the third dose, in males <40 years old. Yet the overall risk remained to be small [44]. Another study from Israel focusing on military personnel showed that the incidence of myocarditis observed one week after receiving the third dose [3.17 (95% CI, 0.64−6.28) per 100,000 vaccines] was lower than observed a week after a second dose of the vaccine in a similar Israeli military population (5.07 per 100,000 vaccines) [45]. Therefore, continued surveillance for any increased risk of myocarditis among Hong Kong adolescents will be needed.

Conclusion

The COVID-19 global pandemic was declared on March 11, 2020 by World Health Organization, and the COVID-19 vaccines were available around one year after the pandemic. While there is mRNA vaccine-related myocarditis, most of these are clinically mild without significant cardiac dysfunction or long-term effects. Only by vaccination can we effectively prevent the severe and fatal outcomes of COVID-19. Until a significant proportion of the population has been protected from proper vaccine coverage, our society cannot return to its normalcy. Therefore, it is crucial to educate the public, promote vaccination in the community and continue monitoring the safety of the available vaccines.

Ethics approval

Not applicable for this review.

Declaration of funding statement

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Conflict of interest

None declared.

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