



Editorial

COVID -19 pandemic and paediatric population with special reference to congenital heart disease

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which belongs to the β -coronavirus genus, is a novel coronavirus first detected in Wuhan, China in December, 2019.¹ The current Corona virus pandemic has seriously threatened the world. The impact of the disease in infants and children is under appreciated. As compared to adults less number of cases have been reported in paediatric population.^{2,3} This article summarises the available information about the effect of COVID-19 infection in children with special emphasis on those with heart disease.

1.1. Lessons from the past

Influenza epidemics have been associated with surge in cardiovascular deaths and other viral and bacterial infections are also known to trigger cardiovascular diseases.^{4,5} The prognosis of many infective diseases is determined by underlying acquired and congenital illnesses.⁶ It is becoming increasingly clear that adult patients with underlying heart disease are at a higher risk of mortality from COVID -19.⁷ It may be speculated, that the children with Congenital heart disease (CHD) may be at a higher risk of complications with COVID 19 similar to adults. Other coronavirus infections in children are usually mild and medical attention is sought in less than 20% cases. Coronaviruses are uncommon cause of Lower respiratory tract infection (LRTI) in children. LRTI after coronavirus infection is more common in younger children (less than 2 years), those with underlying medical conditions (congenital, cardiovascular, genetic or respiratory diseases) and coinfections with rhino viruses. These patients are more likely to be admitted to intensive care units or require respiratory support.^{8,9,10} Previous epidemics of H1N1 influenza and SARS -CoV have taught us that the patients with congenital or acquired heart disease have increased morbidity and mortality related to viral

infections.^{11,12} Due to this, influenza vaccination in CHD patients is recommended as a standard of care.

2. COVID 19 and paediatric population

People of all age groups are susceptible to SARS-CoV-2 infection. However, available epidemiological data mainly from USA and China^{3,13} indicate that children <18 years of age constitute around 1–2% of infected cases. The morbidity and mortality weekly report by CDC, USA revealed that Among 149,082 cases 2572 (1.7%) were children (aged <18 years). Out of 2572 cases mentioned above, information on hospitalization status was available for 33% cases, while information for presence of pre-existing underlying medical conditions and symptoms were available for 13% and 9.4% only. 73% of paediatric patients had symptoms of fever, cough, or shortness of breath as compared to 93% of adults during the same period.³ In a series of 20 admitted patients (65% male) with confirmed COVID-19, Procalcitonin elevation and consolidation with surrounding halo signs were common in paediatric patients which were different from adults. It is suggested that underlying coinfection may be more common in paediatric patients and the consolidation with surrounding halo sign is considered as a typical sign of COVID 19 in paediatric patients.¹⁴ The mean Incubation period in children seems to be longer (6.5 days as compared to 5.5 days) in comparison to adults.² In contrast to adult mortality, mortality figures are very low and very few deaths are reported in children.

The data on impact of SARS-COV-2 on foetus, and on potential of perinatal transmission is scanty. In the past severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus were associated with critical maternal illness, spontaneous abortion, maternal death, severe intrauterine growth retardation, but congenital abnormalities were not reported. There is also no evidence of perinatal transmission of the SARS-associated coronavirus in past. In the current pandemic with COVID-19 no evidence of intrauterine or transplacental transmission from infected pregnant women to their foetuses or congenital malformation was found.^{15,16,17}

Among 345 paediatric cases with information on underlying conditions, 80 had at least one underlying condition. The most common underlying conditions were chronic lung disease (including asthma) (40), cardiovascular disease (25), and immunosuppression (10). 77% of the hospitalized patients and 12% out patients had one or more underlying medical condition.³ Xia et al noted that 35% paediatric patients with COVID-19 infection, had a previous history of congenital or acquired diseases, which may indicate that children with underlying diseases may be more susceptible to

COVID-19 infection. Overall, paediatric patients generally have a good prognosis with an average hospital stay of 12.9 days.¹⁴

Paediatric population affected by COVID-19 appears to have milder symptoms in majority, less frequent severe disease and hospitalizations. Infants and those with underlying co morbidities including CHD are at highest risk of complications of COVID-19. Laboratory findings are similar to adult population with few exceptions. Fever, cough and shortness of breath were less commonly reported in children as compared to adults. Myalgia, sore throat, headache, and diarrhoea were also less commonly reported by paediatric patients.^{3,13,18}

Dong et al classified 2143 paediatric patients with COVID-19 infection as asymptomatic, mild, moderate, severe and critical. 4.4% of their cases were asymptomatic, 50.9% of cases were mild and 38.8% of the cases were in moderate category accounting for 94.1% of all cases. They also noted that the proportion of severe and critical cases was inversely proportional to the age range, with the age group of less than one year constituting 10.6% of the severe and/or critical cases.¹³

Laboratory findings are similar to adult population except that paediatric patients may have high rates of co-infections and procalcitonin elevation.^{14,19–21}

Myocardial injury is being reported frequently in adults. Cases of severe myocarditis with left ventricular systolic dysfunction have been reported in adults.²² During autopsy some of such cases were found to have interstitial infiltration with monocytes in myocardium.²³ In a recently published clinical cohort of COVID-19, acute cardiac injury was seen in 7.2% and arrhythmia in 16.7% of adults and was related with worse prognosis.^{24,25} Weather myocarditis or myocardial injury occurs less commonly in children is not known at present. However from past experiences, corona viruses are known to cause myocarditis in children.²⁶ A new phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection manifesting as a hyperinflammatory syndrome with multiorgan involvement similar to Kawasaki disease shock syndrome has being reported recently from London.²⁷

Why the children are less affected is still not very clear but following may be the contributing factors. Children are made to stay at home and usually well cared for. The exposure to sick is less, that in turn implying that viral load may be less to begin with. Ciaglia et al in their review have elaborated upon the higher circulating levels of ACE 2 in children and asserted that it could offer protection by means of buffering effects and severe infection in elderly could possibly occur due to immunosenescence.²⁸ It is also speculated that children are less sensitive to COVID-19 infection because the maturity and function (e.g., binding ability) of ACE2 in children may be lower than that in adults.¹³ Furthermore, children's immune systems are in developing stage and may respond to challenges differently from adult immune systems. The Immature respiratory tract and immune system in children contributes to severe illness in case of other viral respiratory diseases like influenza or respiratory syncytial virus²⁹ but conflicting reports are there in case of COVID 19. Children may have some peculiar mechanisms which regulate the interaction between the immune system and respiratory machinery. This may be the contributing mechanism for milder COVID 19 disease in children. It may be possible that lung infiltrates may have a protective role in paediatric SARS-CoV-2 infection, similar to lymphocytes participating in inducible bronchus-associated lymphoid structure development after respiratory insult.³⁰ There is also heightened procoagulant activity suggested by elevated D-Dimer levels in children similar to adults.^{18,19}

Consequent to SARS-CoV-2 infection there is upregulation of pro-inflammatory cytokines which causes severe systemic inflammation. This may lead to imbalance between infection induced

increase in metabolic demand and supply. In this adverse milieu patients with congenital heart disease with reduced cardiac reserve may become unstable.

2.1. COVID 19 and congenital heart disease

Children with congenital heart disease (CHD) represent a high risk group because of the limited cardiopulmonary reserve. Management of CHD during COVID-19 is gradually becoming more challenging and its being compromised because of many factors. It is difficult to outline the spectrum of cardiovascular presentations of COVID19 in children however with the currently available knowledge it may be speculated that cardiovascular manifestation may be similar to adults, although the numbers will be less. These presentations range from direct or indirect myocardial injury, myocarditis, possible acute coronary syndrome, cardiac arrhythmias, heart failure and cardiogenic shock.³¹ Hypoxaemia resulting from respiratory insufficiency and cytokine storm triggered by an imbalanced response of type 1 and type 2 helper cells³² are important contributing factors in patient with COVID-19. ACE2 is highly expressed in pericytes of adult human hearts, which indicates an intrinsic susceptibility of heart to SARS-CoV-2 infection.³³ SARS-CoV has been demonstrated to down-regulate myocardial and pulmonary ACE II pathways, mediating myocardial inflammation, lung oedema, and acute respiratory failure due to unabated accumulation of angiotensin II.³⁴ Myocardial injury is an important prognostic factor in COVID -19. Adult patients who had acute cardiac injury (raised cardiac troponins) had higher incidence of complications such as life threatening arrhythmias, multi organ dysfunction, ARDS, systemic coagulopathy and higher mortality,^{31,35} this may be true in children as well.

2.2. Risk stratification

Among the subset of patients with congenital heart disease few might be at a higher risk of decompensation than others based on complexity of disease. The severity of CHD depends not only on anatomic complexity but status of surgical repair and physiologic variables like presence of aortopathy, arrhythmia, end-organ dysfunction, exercise capacity, hypoxemia, cyanosis, NYHA functional class, pulmonary hypertension, hemodynamically significant shunt, venous and arterial stenosis etc. The adult congenital heart disease (ACHD) anatomic and physiological (AP) classification³⁶ elaborates the complexity and heterogeneity of ACHD anatomy and physiology and gives a fairly accurate sense of prognosis. Patients are classified in anatomic stage 1–3 and physiologic stage A to D based on many factors. Patient classified at higher level of severity (anatomic and physiologic stage) are likely to have decreased functional reserve and high risk of SARS-CoV-2 infection related complications.

3. Issues in management

Most of the children with COVID 19 can be managed conservatively and do not require specific treatment. Standard operating procedures for outpatient and inpatients, cardiac catheterization laboratories, operation theatre, echocardiography, which are followed for adult population need to be continued for children population. Teleconsultation, video conferencing and using artificial intelligence for diagnostics and management are to be encouraged whenever possible.³⁷ CHD patient who require emergency/urgent care, admission or percutaneous/surgical intervention may be classified into 3 groups. Confirmed COVID-19 patient, Suspected COVID-19, Patient with Low clinical probability of being a COVID-19 patient/Confirmed non-COVID-19 patient similar to

the classification proposed for adult population.³⁸ This may rationalize the optimal useage of resources at hand. The protocols for diagnosis and management, use of personal protective equipment, procedure and precautions for catheterization laboratories and operating rooms have been well described.^{32,39–41} Although CHD patients are presumed high risk but role of specific anti-viral therapy it still not stabilised at this moment. Antiviral drugs should be used after weighing advantages and disadvantages with caution in children.⁴²

There is no specific cure for SARS-CoV-2 infection and lots of therapies are being under investigation (Remdesivir, Favipiravir, Lopinavir/Ritonavir, Ribavirin, Umifenovir, IFN- α , Nitazoxanide, Camostat mesylate, Chloroquine, Hydroxychloroquine, Anti-inflammatory tocilizumab, Steroids, Anticytokine or immunomodulatory agents, and immunoglobulin therapy etc.)^{42,43,44}

Many of these therapies have cardiovascular side effects especially arrhythmic risk due to QT prolongation. Consequent to the metabolic and pathophysiologic consequences SARS-CoV-2 infection and drug interactions such patients likely to have longer baseline QTc. The risk of risk drug-induced Torsades de pointes is influenced by number of factors such as electrolyte disturbances, female sex, hepatic/renal failure, structural heart disease, congenital long-QT syndromes, and concomitant QT prolonging medications. A risk score has been derived and validated by Tisdale et al⁴⁵ for prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients and this score may be used to risk stratify the patient. Recently Indian Heart Rhythm Society has come up with document regarding cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients and recommendations for its use. It may be applicable to children also.⁴⁶ All these drugs which prolong QT must be given in close monitoring especially to patients of CHD to minimise arrhythmic risk.

Lots of concerns have been raised about the safety of RAAS inhibitors in COVID-19. ACE inhibitors and angiotensin receptor blockers (ARB) may upregulate of ACE2 thereby increasing susceptibility to the virus and hence may cause more severe infection. On the contrary, there is evidence that these drugs may enhance the protective effect of ACE2 on lung. ACE II may be beneficial in patients with lung injury and withdrawal of RAAS inhibitors in certain high-risk patients with known or suspected Covid-19 may be harmful for the patients.^{31,47} The data is currently insufficient to provide any definite recommendation however it is advisable to continue these medications even in children taking them for indications for which the agents are known to be beneficial.

Another important issue is care of children who require intubation or other aerosol generating procedures and at the same time minimising the risk to health care provider (many children may be asymptomatic and unrecognised COVID -19). The consensus guidelines from the Society for Pediatric Anesthesia's Pediatric Difficult Intubation Collaborative and the Canadian Pediatric Anesthesia Society, recommend appropriate personal protective equipment as essential when performing aerosol-generating procedures. Airway procedures should preferably be done in negative pressure rooms. In between surgical cases sufficient time should be allowed for operating room cleaning and air filtration. The goal is to minimize aerosolized respiratory secretions and direct contact with patient. Recommendations include administering anxiolytic medications, intravenous anaesthetic inductions, tracheal intubation using cuffed tracheal tubes and video laryngoscopes and use of in-line suction catheters. Application of prone ventilation is strongly recommended for adult patients, and may be considered for paediatric patients event with CHD with severe ARDS.⁴⁸

4. Conclusions

SARS-CoV-2 infection in majority of children is asymptomatic or mild and progression to severe disease including death is rare. Children with CHD (especially those with complex CHD or decreased cardiac reserve) may be a highest risk of mortality. Urgent action needs to be taken to develop guidelines on risk stratification and management of such patients during COVID-19 pandemic.

Declaration of competing interest

None declared.

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