Cardiology in the Young

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Editorial

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Cardiac workup and monitoring in hospitalised children with COVID- 19

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Abstract

Approximately, 1.7 million individuals in the United States have been infected with SARS-CoV-2, the virus responsible for the novel coronavirus disease-2019 (COVID-19). This has disproportionately impacted adults, but many children have been infected and hospitalised as well. To date, there is not much information published addressing the cardiac workup and monitoring of children with COVID-19. Here, we share the approach to the cardiac workup and monitoring utilised at a large congenital heart centre in New York City, the epicentre of the COVID-19 pandemic in the United States.

SARS-CoV-2, the virus responsible for the novel coronavirus disease-2019 (COVID-19), has infected millions of individuals worldwide with approximately 1.7 million infections in the United States at the time of writing. A growing body of literature has described cardiac manifestations of this disease in adults, including myocarditis and arrhythmias, 2,3 electrocardiographic changes including ST segment elevations, T wave inversions, and laboratory abnormalities such as elevated high-sensitivity troponin T and N-terminal pro-brain-type natriuretic peptide. Although the pathophysiology is unclear, these abnormalities are associated with increased morbidity, such as need for intubation, and mortality. 4-8 Adults have been disproportionately affected, with children making up under 3% of the infected population. ^{1,9} Given the smaller numbers of paediatric cases, there is a paucity of cardiac data available.

While recommendations have been published with regards to general paediatrics, 10 paediatric cardiac catheterisation, 11 cardiothoracic surgery, 12 and pulmonary hypertension, 13,14 there remains a lack of consensus guidelines for non-interventional cardiac workup and monitoring of children hospitalised with COVID-19. In this report, we share our approach to the cardiac workup and monitoring of these children with regards to laboratory, electrocardiographic, and imaging evaluation of children with respiratory presentations of COVID-19 with the goal of increasing awareness of the cardiac manifestations of this disease, suggested diagnostic tests, and when to call the paediatric cardiologist. This was based on our experience at a major congenital heart centre in New York City, the epicentre of the COVID-19 pandemic in the United States. During this time, all paediatric admissions to NewYork-Presbyterian Hospital system sites across New York City were consolidated at Morgan Stanley Children's Hospital. Recently, groups have reported children with COVID-19, or exposure to close contacts with COVID-19, who develop a multi-system inflammatory syndrome. 15,16 The protocols outlined here are intended for application to acute presentation of the "classic" respiratory presentation of COVID-19. Our institution is currently developing a separate multidisciplinary protocol detailing our approach to this new entity, which will be submitted for publication separately.

Criteria for admission at our institution include, but are not limited to, respiratory distress, supplemental oxygen requirement, cardiovascular instability, dehydration, or medications requiring inpatient monitoring. In deciding the appropriate workup, we consider suspicion for cardiac involvement and acuity level (Table 1).

Children without suspicion for cardiac involvement

Patients with normal blood pressure and cardiac exam, absence of hepatosplenomegaly, normal cardiac size on chest X-ray, normal high-sensitivity troponin T and N-terminal pro-brain-type natriuretic peptide, and who do not meet criteria for multi-system inflammatory syndrome can be considered low risk for cardiac involvement. All children with confirmed or suspected COVID-19 should have basic laboratory studies drawn according to their institution specific protocol, but should include at least a complete blood count with differential, electrolytes, renal

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Table 1. Cardiac workup and monitoring in children with and without suspicion for cardiac disease

for cardiac disease	Children with suspicion for cardiac disease
institution protocol CBC with differential Chemistry ESR/CRP Ferritin Procalcitonin D-dimer Fibrinogen LDH	Baseline Labs Plus: hs-Troponin T q24–72h NT-proBNP q24–72h Cardiac monitoring: Assess arrhythmia burden 15 Lead ECG to assess for: Myocarditis Rhythm disturbance Baseline QTc, T waves, and ST segments Echocardiogram: at discretion of cardiologist including: Ventricular function Valvar regurgitation Pericardial effusion Proximal coronary arteries Additional views if high suspicion of structural or congenital heart disease

 $\label{eq:cbc} CBC = complete blood count; CRP = C-reactive protein; ECG = electrocardiogram; \\ ESR = erythrocyte sedimentation rate; hs-Troponin T = high-sensitivity troponin T; \\ IL-6 = interleukin 6; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro-brain-type natriuretic peptide$

and liver function tests, erythrocyte sedimentation rate, and C-reactive protein. In addition, a screening high-sensitivity troponin T and N-terminal pro-brain-type natriuretic peptide should be measured in all admitted children. A chest X-ray is useful in assessing cardiac size, confirming clinically suspected pneumonia, and evaluating respiratory failure, and should be obtained for children admitted with COVID-19.

We do not obtain routine electrocardiograms or echocardiograms for children with acute respiratory presentations of COVID-19 without suspicion for cardiac disease given the added exposure to staff. However, an electrocardiogram should be obtained for patients requiring ICU admission, as well as prior to starting therapy with corrected QT interval (QTc) prolonging medications, such as hydroxychloroquine, azithromycin, and lopinavir/ritonavir, 17 regardless of suspicion for cardiac involvement. Because the QTc appears to achieve peak prolongation between days 3 and 4 of treatment¹⁸ and hydroxychloroquine has a long half-life, 19 these patients should continue to have their QTc monitored after completing the medication course. Due to a recent study showing increased rates of arrhythmia and mortality with hydroxychloroquine use,²⁰ its role in the treatment of children with severe COVID-19 is unclear. However, since the impact of other experimental therapies such as remdesivir is not yet known, we suggest close monitoring of the QTc even in the absence of hydroxychloroquine use.

In cases where hydroxychloroquine is still being used, published recommendations suggest that the QTc should be less than 500 ms for patients with normal QRS durations and less than 520 ms for patients with prolonged QRS durations prior to initiating therapy. If the QTc is borderline (460–500 ms), treatment may be initiated with caution. ^{18,21}

More frequent monitoring of the QTc may be warranted in patients with comorbid conditions known to prolong the QTc, including congenital long QT syndrome, severe renal insufficiency,²² treatment with other QTc prolonging medications, and

electrolyte disturbances such as hypokalaemia, hypomagnesemia, and hypocalcemia. Electrolyte abnormalities should be corrected prior to initiating QTc prolonging therapies and electrolytes should be closely monitored for the duration of therapy. Concurrent use of other QTc prolonging medications should be avoided.

Children with suspicion or at risk for cardiac involvement

Growing evidence suggests common involvement of multiple organ systems including the heart, kidneys, and brain. ^{23–26} There are many situations for which the paediatric cardiology team might be consulted. These may include abnormal physical exam findings suggestive of heart failure, such as inappropriate tachycardia or arrhythmia, gallop, pericardial friction rub, or jugular venous distention, evidence of cardiogenic shock, or pulmonary hypertension. Elevated high-sensitivity troponin T or N-terminal pro-brain-type natriuretic peptide or cardiomegaly on chest X-ray also warrant a cardiology consult. The paediatric cardiologist may also be consulted for abnormal electrocardiogram, including changes associated with pericardial or myocardial inflammation.

Patients who are at risk for severe infection and may be more likely to require admission to the ICU include infants and those with underlying comorbidities such as lung disease, cardiovascular disease, chronic kidney disease, diabetes, and metabolic or immune disorders.^{27,28} Based on consensus opinion at our institution, we suggest that special consideration should be given to patients with pulmonary hypertension, unrepaired complex congenital heart disease, cyanotic heart disease with oxygen saturations less than 85%, ventricular dysfunction requiring medical therapy, and history of heart transplantation on immunosuppressive medications. Due to their higher risk profile, these patients may warrant a more complete evaluation than those without pre-existing conditions.

Laboratory studies

In accordance with institutional COVID-19 protocol, children with confirmed or suspected acute COVID-19 requiring admission undergo laboratory workup including complete blood count, chemistry, inflammatory markers, high-sensitivity troponin T, and N-terminal pro-brain-type natriuretic peptide. In our experience, for children with suspected cardiac involvement, it is useful to trend high-sensitivity troponin T and N-terminal pro-brain-type natriuretic peptide every 24–72 hours. If these are grossly abnormal or continuing to rise, we obtain an electrocardiogram and echocardiogram and consider transfer to the ICU, if not already admitted there.

Electrocardiography/reviewable cardiac monitoring

Children with suspicion for cardiac involvement or multi-system inflammatory syndrome should have a screening electrocardiogram to assess for myocarditis or arrhythmia and establish a baseline for QTcs, T waves, and ST segments. If the electrocardiogram has findings suggestive of ischaemia or inflammation, such as T-wave inversions or ST segment elevations or depressions, we suggest obtaining electrocardiograms daily until the abnormalities resolve or the clinical situation has improved. All patients with suspicion for cardiac involvement, as well as those admitted to the ICU, should be placed on reviewable cardiac monitoring to assess arrhythmia burden.

Cardiology in the Young 909

Echocardiography

The decision to perform an echocardiogram is made at the discretion of the paediatric cardiologist based on clinical, laboratory, and electrocardiographic data, with careful consideration given to reducing viral exposure for staff in the setting of widespread infection. At our institution, we developed a protocol for focused studies, keeping in mind the following goals such as assess for signs of myocarditis or myocardial dysfunction, evaluate for evidence of pulmonary hypertension/pulmonary embolus, and minimise exposure to the sonographer. We suggest obtaining an echocardiogram for those children with suspicion for cardiac involvement, including those with physical examination findings concerning for heart failure, abnormal laboratory values or electrocardiograms with evidence of myocardial injury, or who present with multi-system inflammatory syndrome. Our current protocol includes assessment of ventricular function, valvar regurgitation, presence of pericardial effusion, and, with the newly described multi-system inflammatory syndrome in children^{15,16} in mind, evaluation of the proximal coronary arteries in children with confirmed or suspected COVID-19 who require an echocardiogram. Children with known or suspected congenital heart disease should have a complete congenital transthoracic echocardiogram performed when necessary. In order to limit staff exposure, all measurements are done after the sonographer has left the patient room.

Although extracorporeal membrane oxygenation use appears to be infrequent in children with COVID-19,²⁹ there is evidence that it may provide a survival benefit for adults with severe infection,³⁰ though its use is not consistent across all centres.³¹ In this situation, echocardiography may be required to assess cannula position, ventricular function, and presence of left atrial hypertension.

In our opinion, following hospital discharge, a complete follow-up echocardiogram is recommended in the out-patient setting for those children with abnormalities on the initial study. The optimal timing of follow-up has yet to be established and will be determined primarily by considering the clinical context as well as staff exposure and facility capacity in the setting of the evolving pandemic.

Arrhythmia

Arrhythmia has been reported as a significant issue in adult patients with COVID-19^{2,3} and may be secondary to myocardial injury or direct effects of cytokines on sodium and potassium channels.³² Interleukin-6 has been shown to be elevated in those with myocardial injury compared with those without.³³ These same cytokines may also inhibit enzymes required for clearing certain QTc prolonging medications, thereby enhancing their impact on the QTc.³¹ Other potential etiologies for arrhythmia include metabolic disturbance,³⁴ hypoxia,³⁵ and genetic dysrhythmias, which may be revealed by acute illness or significant stressors, such as Brugada syndrome³⁶ and long QT syndromes.³⁷ If there is an associated elevation in high-sensitivity troponin T, early myocarditis should be considered.³⁸ Due to the risk of arrhythmia, we suggest that these patients be placed on reviewable cardiac monitoring.

Limitations

Significant limitations exist that may impact the relevance of this approach, most importantly that the practices outlined in this report are based primarily on expert opinion and adult literature rather than paediatric data. The number of children with COVID-19

worldwide is small relative to the number of adults and our understanding of it is evolving rapidly, resulting in relatively limited data addressing paediatric cardiac involvement. Prospective data collection is necessarily impeded by the need to minimise exposure of phlebotomy, electrocardiogram, and echocardiogram staff. Furthermore, the natural history and underlying pathophysiology of this disease in children, including the newly emerging multisystem inflammatory syndrome in children, is just now being described. These practices reflect our best understanding at the time of writing; however, our knowledge of this disease and its various presentations is constantly evolving and clinical practice must necessarily evolve in-kind.

Conclusions

Providers caring for children with acute COVID-19 should keep cardiac involvement in mind and consult paediatric cardiology when there is suspicion for cardiac injury. In our opinion, the extent of workup and monitoring of these patients should be based on careful determination of clinical suspicion for cardiac disease and level of acuity of each patient, as well as the expected impact the information will have on clinical management. As the full picture of the multi-system inflammatory syndrome in children emerges, the role of the paediatric cardiologist will likely evolve and indications for testing may change. More information obtained from multi-centre collaboration is needed to establish definitive guidelines.

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Conflicts of Interest. None.

References

- Cases in the U.S. Centers for Disease Control and Prevention Website, 2020. Retrieved May 27, 2020 from https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061–1069. doi:10.1001/jama.2020.1585
- Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in NYC. Commentary. NEJM 2020; 382: 2372–2374. doi: 10.1056/ NEJMc2010419
- Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol 2020. [Epub ahead of print].
- Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020; e200950.
- Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020. doi:10.1001/jamacardio.2020.1017
- Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020.
- Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. J Card Fail 2020.

- Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics 2020; e20200702. doi: 10.1542/peds.2020-0702
- Carlotti APCP, Carvalho WB, Johnston C, Rodriguez IS, Delgado AF. COVID-19 diagnostic and management protocol for pediatric patients. Clinics (Sao Paulo) 2020; 75: e1894. doi:10.6061/clinics/2020/e1894
- Morray BH, Gordon BM, Crystal MA, et al. Resource allocation and decision making for pediatric and congenital cardiac catheterization during the novel coronavirus SARS-CoV-2 (COVID-19) pandemic: A U.S. Multi-institutional perspective. J Invasive Cardiol 2020; 32: E103–E109.
- Ryan JJ, Melendres-Groves L, Zamanian RT, et al. Care of patients with pulmonary arterial hypertension during the Coronavirus (COVID-19) pandemic. Pulm Circ 2020; 10: 1–7. doi: 10.1177/2045894020920153
- Stephens EH, Dearani JA, Guleserian KJ, et al. COVID-19: crisis management in congenital heart surgery. World J Pediatr Congenit Heart Surg 2020; 1–6. In press.
- Horn E, Chakinala M, Oudiz R, Joseloff E, Rosenzweig EB. Could pulmonary arterial hypertension (PAH) patients be at a lower risk from severe COVID-19? Pulm Circ 2020; 10(2): 1–2. doi: 10.1177/2045894020922799
- Jones CG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr 2020. doi:10.1542/hpeds.2020-0123
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory schock in children during COVID-19 pandemic. Lancet 2020. doi:10.1016/S0140-6736(20)31094-1
- Naksuk N, Lazar S, Peeraphatdid T. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. Eur Heart J Acute Cardiovasc Care 2020; 1–7. doi:10.1177/2048872620922784
- Chorin E, Dai M, Shulman E, et al. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. MedRxiv 2020. doi: 10.1101/2020.04.02.20047050
- Plaquenil hydroxychloroquine sulfate tablets, USP. Food and Drug Administration Website, 2020. Retrieved May 6, 2020 from https://www. accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf
- Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a mulitnational registry analysis. Lancet 2020. doi:10.1016/S0140-6736(20) 31180-6
- Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). May Clin Proc 2020. doi:10.1016/j.mayocp.2020.03.024
- Malhis M, Al-Bitar S, Farhood S, Zaiat KA. Changes in QT intervals in patients with end-stage renal disease before and after hemodialysis. Saudi J Kidney Dis Transpl 2010; 21: 460–465.
- Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect 2020. doi:10.1016/j.nmni.2020.100669
- Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology 2020; 158: 1518–1519.

- Liu R, Ming X, Zhu H, et al. Association of cardiovascular manifestations with in-hospital outcomes in patients with COVID-19: a hospital staff data. medRxiv 2020. doi:10.1101/2020.02.29.20029348
- Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 2020; 55: 105924.
- Shen KL, Yang YH, Jiang RM, et al. Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition). World J Pediatr 2020. doi:10. 1007/s12519-020-00362-4
- Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and metaanalysis. Int J Infectious Diseases 2020; 91–95. doi:10.1016/j.ijid.2020. 03.017
- Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and canadian pediatric intensive care units. JAMA Pediatr 2020. doi:10.1001/jamapediatrics.2020.1948
- Jacobs JP, Stammers AH, St Louis J, et al. Extracorporeal membrane oxygenation in the treatment of severe pulmonary and cardiac compromise in COVID-19: experience with 32 patients. ASAIO J 2020. doi:10.1097/MAT. 0000000000001185
- Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020. doi:10.1016/S0140-6736(20) 31189-2
- Lazzerini PE, Boutjdir MB, Capecchi PL. COVID-19, arrhythmic risk and inflammation: Mind the gap! Circulation 2020. doi: 10.1161/ CIRCULATIONAHA.120.047293
- 33. Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz 2020. doi:10.1007/s00059-020-04909-z
- Chen Y, Guo X, Sun G, et al. Effect of serum electrolytes within normal ranges on QTc prolongation: a cross-sectional study in a Chinese rural general population. BMC Cardiovasc Disord 2018; 18: 175. doi:10.1186/ s12872-018-0906-1
- Clark RE, Christlieb I, Sanmarco M, Diaz-Perez R, Dammann JF. Relationship of hypoxia to arrhythmia and cardiac conduction hemorrhage: an experimental study. Circulation 1963; 27: 742–747. doi: 10.1161/01.CIR.27.4.742
- 36. Rattanawong P, Vutthikraivit W, Charoensri A, et al. Fever induced Brugada syndrome is more common than previously suspected: a cross-sectional study from an endemic area. J Am Coll Cardiol 2015; 65 (10 Supp): A430.
- 37. Shwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ: Arrhyth Electrophysiol 2012; 5: 868–877.
- Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation 1997; 95: 163–168.