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VIEWPOINTS

Myocarditis After COVID-19 Vaccination in Pediatrics: A Proposed Pathway for Triage and Treatment

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On December 11, 2020, the US Food and Drug Administration granted emergency use authorization for the Pfizer-BioNTech mRNA based COVID-19 vaccine for individuals aged ≥16 years, followed by extension of this authorization to children ages 12 to 15 years on May 10, 2021[1] and to ages 5 to 11 years on November 2, 2021. As vaccination numbers accelerated in these age groups, pediatric vaccine recipients began presenting with features meeting the Centers for Disease Control and Prevention (CDC) definition of myocarditis,[2] including chest pain, laboratory evidence of myocardial inflammation, and, in some cases, characteristic findings suggestive of myocardial edema and fibrosis on cardiac magnetic resonance imaging (MRI). The CDC and Food and Drug Administration have determined a causal link is likely between the mRNA vaccines (ie, Pfizer-BioNTech, Moderna) and myocarditis.[2] Though this is a rare complication (70.7 and 105.9 cases in adolescent males per million doses of Pfizer-BioNTech vaccine in ages 12–15 and ages 16–17, respectively)[3] more cases of post-vaccine myocarditis/myopericarditis are anticipated as more adolescents and younger children become vaccinated. With the goal of standardizing care and reducing variability, while still ensuring safety, we propose this pathway to guide decision-making about triaging, testing, and treatment for all providers involved in the care of these patients, beginning in the emergency department, where most (if not all) patients will be triaged (Figure). We believe our pathway can be applied at all centers including those without immediate access to certain cardiology testing modalities (eg, continuous telemetry, pediatric echocardiography services, cardiac MRI). The terms myocarditis and myopericarditis (ie, myocarditis accompanied by inflammation of the pericardium) have been used interchangeably in the literature, and herein we follow the CDC convention of using myocarditis to include myocarditis, pericarditis, and myopericarditis.[2,4–9]

As pediatric providers sought to understand the pathophysiology of this unusual phenomenon and whether there was a true cause and effect based on the dates of vaccination and onset of symptoms, a wide range of management was used based on prior experience with pediatric myocarditis. Most patients were admitted for observation while some were followed as outpatients. Some received NSAIDs only, and others received additional immune-therapies including intravenous immunoglobulin (IVIG) and systemic corticosteroids. In addition to routine cardiac testing with ECGs and echocardiograms, many, but not all, patients underwent cardiac MRI with contrast. Despite the wide variation in management, which remains provider and center-specific, to date, the overwhelming majority of these patients have recovered clinically and have been discharged home within 10 days or less with

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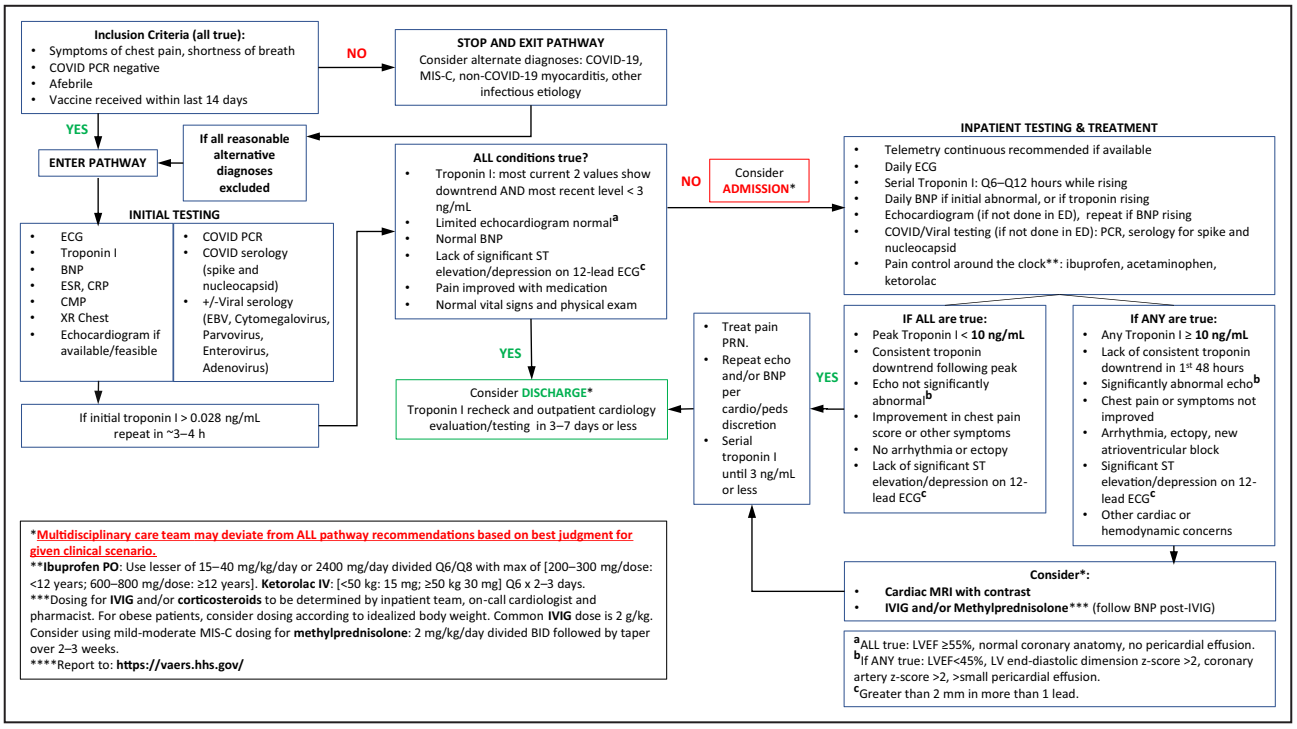

Figure. Pathway for myocarditis after COVID-19 vaccine.
BID indicates twice a day; BNP, brain natriuretic peptide; CMP, comprehensive metabolic panel; COVID, coronavirus disease; CRP, C-reactive protein; EBV, Epstein–Barr virus; ED, emergency department; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; LV, left ventricle; LVEF, left ventricular ejection fraction; MIS-C, multisystem inflammatory syndrome in children; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; and XR, x-ray.

no residual echocardiographic evidence of significant cardiac dysfunction.[4–9] These patients are now undergoing close outpatient cardiology follow-up and testing to understand if there are significant long-lasting sequelae. The CDC is also investigating the long-term effects of COVID-19 vaccination associated myocarditis through surveys of patients and healthcare providers.

In our pathway, we have carefully selected specific criteria we believe can help reduce the number of unnecessary hospital admissions, shorten the length of inpatient hospitalization, and limit the use of potentially unnecessary and costly treatment and testing. To enter the pathway, a clear case definition must be developed. Our own collective unpublished experience along with published case series suggest that the great majority of symptoms manifest in children between 1 to 4 days from the date of vaccine administration (more commonly after the second dose).[4–9] A multicenter adult study showed a latency period of up to 10 days post-vaccine administration.[10] We believe 14 days is a reasonable time frame where the development of myocarditis secondary to the vaccine might be detected, and our proposed initial testing (already widely performed) would help satisfy the CDC definition for probable myocarditis.[2] While some cases will fall outside this time frame[4,5] we suggest making COVID-19 vaccine related myocarditis a diagnosis of exclusion in such instances only after other diagnoses (eg, COVID-19 disease, multisystem inflammatory syndrome in children, non-COVID-19 myocarditis, other infectious causes) have been methodically considered and excluded first. Beyond 21 days, post-vaccine induced myocarditis is still plausible but much less likely.

Our pathway next delineates selection criteria for admission from the emergency department. Currently, most patients with post-vaccine myocarditis are admitted for observation, treatment and, in some cases, additional testing.[4–9] However, inpatient observation may not always be necessary, and we agree with the approach adopted by some that not all patients require admission[5] so long as certain clinical criteria can be satisfied: reassuring and downtrending troponin I values, normal ECG, normal limited echocardiogram, and improvement in symptoms. Given that on-call pediatric echocardiography may not be immediately available at all locations, it is reasonable for an adult-trained sonographer to perform a limited/focused survey to at least ensure normal left ventricular (LV) systolic function, normal coronary artery anatomy, and no pericardial effusion. Although not a specific marker for active myocarditis, troponin testing should be undertaken in all suspected cases. The prognostic utility of troponin

in forecasting the clinical course of patients with myopericardial inflammation is not clear.[11–13] In a small group of teenagers with myopericarditis who exhibited double-digit troponin I elevation (in 1 case peaking as high as 134 ng/mL), all patients had normal LV systolic function throughout a 2-month median follow-up period and were treated with only NSAIDs.[13] Data from a more recent multicenter pediatric myocarditis analysis show that troponin I level correlated poorly with the degree of ventricular dysfunction (paradoxically lower with moderately severely reduced function) as well as the presence/absence of cardiac inflammation.[12] However, elevated levels were associated with poor outcomes in the subset of patients with normal LV systolic function on echocardiogram.[11]

We propose using a troponin I threshold of 3 ng/mL to help determine who can safely be discharged from the emergency department and be observed as an outpatient so long as a downtrend can be demonstrated. This threshold was chosen based in part on our unpublished early experience with patients we cared for in May and June 2021. Several adolescents presented with abnormal but not markedly elevated troponin I levels (between 1 and 3 ng/mL) and had normal echocardiograms before ultimately discharging home for outpatient follow-up. Among patients who were admitted, most had a slow decline of troponin I as their symptoms improved and remained hospitalized until the level approached 3 ng/mL or less. No patient had a normal troponin I level (defined at our institution as <0.028 ng/mL) at the time of hospital discharge, and most eventually normalized as outpatients; some patients were lost to follow-up, and in other cases levels only completely normalized several months later.

The decision on first-line agent for treatment of inpatients is challenging in part because of provider preferences based on the perceived risk–benefit profile for patients. We propose beginning treatment with NSAIDs, the most commonly reported therapy to date, with or without acetaminophen to control pain and minimize patient discomfort (ie, analgesia) while waiting for inflammation to peak and then subside. Recognizing that NSAIDs have adverse effects (eg, gastritis, acute kidney injury), we offer specific dosing recommendations and urge taking care to use the lowest effective dose when possible and not to exceed the maximum daily recommended dose (Figure). We propose multiple parameters to help determine which admitted patients may benefit from additional immunomodulatory treatment beyond NSAIDs such as IVIG and/or corticosteroids (prednisone or methylprednisolone). We suggest using a troponin I threshold of ≥10 ng/mL based on a multicenter study of patients with prepandemic pediatric myocarditis, who similarly to most patients with post-COVID-19 vaccine myocarditis, all had normal LV systolic function on admission.[11] Patients who experienced worse clinical outcomes (eg, use of heart failure medications, mechanical ventilation, death/transplant) had a double-digit average troponin I level compared with those who did not (18.2 versus 6.4 ng/mL).[11]

Other factors for escalation of therapy would include lack of improvement in symptoms/chest pain, lack of consistent downtrend of troponin level in first 48 hours, and significant abnormalities on ECG and echocardiogram as outlined in Figure. In the published case series of myocarditis after mRNA COVID-19 vaccination to date, most patients had either normal echocardiograms or mild abnormalities such as mildly depressed LV systolic function (ejection fraction 45%–54%) and sometimes small pericardial effusions.[4–9] More significant findings such as moderate or severe LV systolic dysfunction and coronary abnormalities were reported but at much lower frequencies.[4,6] Normalization or near-normalization of LV systolic function was reported in most studies.[4–7,9] Taken together, we advocate for IVIG and/or corticosteroids use only for significant (eg, left ventricular ejection fraction <45%), not for mild echocardiogram abnormalities. ECG criteria were specified keeping in mind that mild ST elevation consistent with early repolarization, a common and benign finding, could be mistaken for pathologic ST elevation in the context of elevated troponin, and that most reports do not quantify the severity of ST elevation.

Although IVIG and corticosteroids continue to be used frequently to treat pediatric myocarditis and are now also being used for post-vaccine myocarditis, the effects on clinical outcomes (eg, overall survival, improvements in LV size and function) for both conditions are unknown at this time. As previously stated, we encourage initiating treatment first with cautious use of NSAIDs and avoidance of IVIG and/or corticosteroids in patients with pediatric post-vaccine myocarditis who are demonstrating a clear trend towards clinical improvement within 48 hours after presentation (or after initiation of NSAIDs treatment). Large randomized controlled trials for pediatric myocarditis are lacking, leaving insufficient evidence to allow for uniform recommendations.[14,15] Data from 1 prepandemic multicenter retrospective pediatric myocarditis study suggested a possible rescue benefit of IVIG for patients with evidence of inflammation (positive MRI or biopsy). These patients, who had depressed LV systolic function at admission (shortening fraction 17.8%), experienced recovery in function by the time of discharge (improved to 31%).[12] However, those who received IVIG had worse ventricular function compared with patients with non-IVIG indicating a treatment bias. Patients with depressed function were also not randomized to treatment thereby precluding a direct comparison of clinical trajectory/recovery with or without IVIG. As the authors acknowledge, the high frequency of use of IVIG and corticosteroids and the low incidence in general of death, transplant, and

cardiac-related readmissions limits the ability to draw definitive conclusions. Further, generally ventricular function recovers fully in many patients with myocarditis making it difficult to discern a true treatment effect.[14] Likewise, the benefit of immunosuppressive treatment of myocarditis after COVID-19 vaccination is unclear. In the largest case series to date comprising 139 patients aged <21 years with probable/confirmed myocarditis following COVID-19 vaccination, depressed ventricular function was present in 26 cases and had normalized in 25 of 26 by the time of publication.[4] IVIG and corticosteroids were used in 30 patients, but it was not reported how many of these treated patients had depressed ventricular function. It is also not clear whether use of IVIG and corticosteroids hastened overall clinical recovery or shortened hospital length of stay.

In a recent multicenter study of adults (interquartile range, age 40–70 years) who developed myocarditis after receiving the Pfizer-BioNTech or Moderna vaccines, most patients were treated with NSAIDs alone and were discharged after a median stay of just 2 days.[10] No patients were treated with corticosteroids or IVIG, although 9 of 20 patients were treated with colchicine, an agent not routinely used in the treatment of pediatric myocarditis but used in adults. The swift recovery of these adults, some with comorbidities that are rarely present in otherwise healthy adolescents (eg, hypertension, alcohol/drug dependence, diabetes, coronary artery disease, cancer, chronic kidney disease), helps support the notion that corticosteroids and IVIG may not always be necessary for COVID-19 vaccine–related myocarditis in the pediatric/adolescent population.

Our pathway also incorporates guidance on cardiac imaging. Cardiac MRI, if available, has been obtained in many centers during the diagnostic evaluation of postvaccine myocarditis,[4–9] but the clinical value of such data remains uncertain. Pre-COVID-19 pandemic data show that persistence of myocardial fibrosis and in some cases ongoing inflammation in some patients with asymptomatic adolescent myocarditis can be seen at least 6 to 12 months from the initial episode even when troponin levels, ECG changes, and LV systolic function have returned to normal—well beyond the traditional 3- to 6-month window of activity restriction.[16] The clinical significance of these persistent radiologic findings, particularly relating to the safety of resuming strenuous physical activities is unclear, especially given that many patients will not undergo repeat MRI testing after normal exercise stress testing. There is potential for abnormal MRI findings during the initial episode to trigger additional cardiac MRIs that may be unnecessary and result in undue emotional and financial burdens for patients and families. There may also be a lack of availability of pediatric cardiac MRI testing and protocols in some pediatric centers, leading to potentially disruptive and costly transfers to other centers.

With these challenges in mind, we suggest performing a cardiac MRI with contrast in cases where there is clinical worsening, or where there is an unclear or lagging trend towards clinical resolution (Figure). If cardiac MRI is undertaken, we recommend the following simple and quick myocarditis protocol, preferably on a 1.5 Tesla magnet, to maximize diagnostic yield: a short axis stack, 4 chamber, 3 chamber, 2 chamber, and left ventricular outflow tract steady state free precession; aortic and pulmonary valve steady state free precession, and velocity encoded cine; pre-contrast T2-weighted myocardial edema imaging, T1-weighted and T2-weighted mapping; first pass coronary perfusion in 3 short axis planes (apical, mid, basal); late gadolinium enhancement at 5 and 10 minutes in short-axis, 4 chamber, 3, chamber, 2 chamber; and postcontrast whole heart 3-dimensional navigator gated coronary arteries. For more information, please refer to the following 2020 protocol,[17] 2009 *Journal of the American College of Cardiology* white paper,[18] and an update from 2013.[19]

In conclusion, as the COVID-19 pandemic continues to evolve, so does the presentation of children seeking care for COVID-19 related complaints. Acknowledging that our understanding of myocarditis after COVID-19 vaccination (and myocarditis in general) is incomplete, we believe there are still opportunities to help reduce and eliminate unnecessary variations in management thereby improving overall care quality. We envision our pathway and recommendations as a dynamic tool, evolving as new information becomes available, and we hope that it will provide practical guidance in the interim. As with any guideline, there is still the freedom to deviate based on best clinical judgment. More widespread adoption of a standardized approach as proposed here will aid in the long-term study of these patients, less mixed messaging to our patients, caregivers, and other care providers, and decreased use of expensive and less ubiquitous resources such as cardiac MRI as we strive to put this pandemic behind us.

ARTICLE INFORMATION

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