Letter to the Editor

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Laboratory findings in a child with SARS-CoV-2 (COVID-19) multisystem inflammatory syndrome

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To the Editor,

A 30-month-old male presented after 6 days of fever with decreased activity dry and cracked lips, conjunctival injection, and a macular rash on his soles. Vital signs were remarkable for fever (41.2 °C), tachypnea, and tachycardia (rate=156). He was responsive to voice, but had delayed capillary refill time and decreased skin turgor. Ultrasound heart, inferior vena cava, and lungs revealed diminished cardiac contractility, moderate hypovolemia, and absence of B lines (no pulmonary edema). See Table 1 for contributory laboratory values, including an increased cardiac troponin (cTn). COVID PCR was positive, and COVID antibodies (total IgG, IgM, IgA; nucleocapsid) changed from non-reactive to reactive during the hospital stay.

He was administered 25 mL/kg of intravenous lactated ringer's solution, with subsequent improved heart rate and perfusion, and admitted for presumed COVID-19 multisystem inflammatory syndrome in children (MIS-C). Formal echocardiogram showed reduced left ventricular ejection fraction (LVEF) of 46%, dilated left main and left anterior descending coronary arteries with Z-scores of +2.8 and +3.5, respectively (consistent with small coronary aneurysm), and diastolic run off into the abdominal aorta suggesting low

Table 1: Initial laboratory values.

Laboratory value	Result	Reference range (for age)
Cardiac troponin I (Abbott)	0.306 µg/L, remained steady state	0.030 µg/L
NT-proBNP	1420 ng/L	5–390 ng/L (2–6 years)
Sodium	129 mmol/L	135–148 mmol/L
Hemoglobin	9.9 g/dL	11.5–13.5 g/dL (2–6 years)
Blood urea nitrogen	24 mg/dL	4–19 mg/dL
Creatinine	< 0.57 mg/dL	0.24–0.41 mg/dL
Erythrocyte sedimentation rate	84 s	0–20 mm/h (age<50)
C-reactive protein	233.05 mg/L	<5.00 mg/L
Procalcitonin	54.6 µg/L	0.10–0.49 ng/mL (for child)
Lactate	1.8 mmol/L	0.07–2.1 mmol/L
D-dimer	775 ng/mL	0–229 ng/mL
Lactate dehydrogenase	18 U/L	120–300 U/L
Ferritin	80.9 µg/L	30.0–400.0 ng/mL
Absolute lymphocyte count	$1.1 \times 10^3/\text{mm}^3$	(1.6–10.5)
Transaminases, bilirubin, albumin	All normal	

systemic vascular resistance. He immediately received intravenous immunoglobulin (IVIG) and 24 h of high dose methylprednisolone, high dose aspirin, and enoxaparin for thromboprophylaxis due to the increased D-dimer. A few days after admission, his LVEF improved to 76%. As his inflammatory markers improved, he did not require the immunosuppressive agent anakinra. He was discharged after 7 days.

MIS-C COVID Centers for Disease Control definitions is based on all 4 of [1–5]:

(1) Age <21 years; (2) Clinical presentation with all of the following: (a) fever ≥ 38.0 °C for ≥ 24 h; (b) laboratory evidence of inflammation, including any of: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), interleukin 6, neutrophilia, lymphopenia, hypoalbuminemia; (c) multisystem (≥ 2)

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organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); (d) clinically severe illness requiring hospitalization; (3) No alternative plausible diagnoses; (4) Recent SARS-CoV-2 exposure within 4 weeks, or infection as proven by RT-PCR, serology, or antigen test.

This toddler's constellation of signs and symptoms with reduced systolic function, dilated coronary arteries consistent with small aneurysm, and increased cTnI and NT-proBNP was diagnostic of MIS-C secondary to COVID-19. SARS-CoV-2 is unique in that it has a relatively benign course in children despite high levels of nasopharyngeal viral RNA of SARS-CoV-2 in infected children, suggesting a permissive state for viral replication. MIS-C was first described in Europe in April 2020. The majority with MIS-C have fever and abdominal pain with increased cTnI, NT-proBNP, decreased LVEF, and coronary dilation. In a systematic review of 662 patients (11 deaths, 147 mechanically ventilated, 398 with shock), 281 had cTn measured and mean cTn was 494 ± 37 ng/L [6]. However, neither the assay type (cTnI or cTnT) nor manufacturer were specified, a common problem in the COVID literature [7]. Echocardiogram was done in 88%, of whom 45% had depressed LVEF and 15.7% had coronary aneurysm with or without dilation. They identified laboratory findings associated with MIS-C due to SARS-CoV-2, but not associated with standard pediatric SARS-CoV-2 infection, including D-dimer, fibrinogen, and other inflammatory markers. They did not compare troponin levels between the two entities in spite of the fact that cardiac complications are most feared in MIS-C.

The data on laboratory abnormalities in children with severe SARS-CoV-2 infection in the absence of MIS-C are sparse and inconsistent, but CRP, procalcitonin, and LDH were frequently increased [8]. In mild disease, creatine kinase-MB was frequently increased and may be indicative of cardiac injury [8].

In MIS-C, the majority of children described have been discharged to home after one week [2–4], and some aspects of MIS-C are similar to Kawasaki Disease (KD): prolonged fever, multisystem inflammation, lymphadenopathy, diarrhea, meningismus and high inflammatory biomarkers [5]. Differences from KD raise the question whether MIS-C is KD with SARS-CoV-2 as the trigger, or if it is distinct. Most are serology IgG positive rather than PCR positive, suggesting MIS-C is a post-infectious inflammatory state. Furthermore, KD associated with COVID-19 is reported to be more likely to have elevated troponin or BNP than classical KD [9].

Measurement of cardiac and inflammatory biomarkers in COVID-19 patients is important [10–14]. Among adults

with SARS-CoV-2, cTn testing facilitates risk stratification, and may assist in utilization of imaging and disease management; cTn concentrations >99th percentile are indicative of myocardial injury and portend a poor outcome in non-pediatric COVID-19 patients. The incidence and degree of myocardial injury in COVID-19 varies and may be largely dependent upon disease severity, definition of myocardial injury, and contemporary vs. high sensitivity cTn assay. Myocardial injury is related to the severity of illness and the cTn concentration. A baseline or isolated cTn result in a COVID-19 patient may be utilized for risk stratification, monitoring progression of myocardial injury, or prognostication of morbidity and mortality. In Covid-19 patients, an increased baseline cTn is independently associated with higher likelihood of need for mechanical ventilation (22 vs. 4%), and development of acute respiratory distress syndrome (59 vs. 15%), and acute kidney injury (9 vs. 0%); 12–69% of patients are reported to have increased cTn, regardless of assay. Serial hs-cTn helps to monitor disease progression, particularly when sex-specific 99th percentiles are appropriately reported.

Natriuretic peptides are biomarkers of myocardial stress and are frequently increased among patients with severe respiratory illnesses even in the absence of elevated filling pressures or clinical heart failure. Much like cTn, increased BNP or NT-proBNP is associated with an unfavorable course among COVID patients with acute respiratory distress syndrome. After adjusting for potential confounders, NT-proBNP was an independent risk factor for in-hospital death in patients with severe COVID-19 [14]. The cutoff value of NT-proBNP to predict the adverse outcome of severe COVID-19 patients (88 ng/L) was far lower than the threshold to diagnose heart failure. NT-proBNP monitoring to follow the extent of cardiac stress and inflammation may be useful for early disease severity prognostication.

Inflammatory biomarkers have been useful measures during acute COVID-19 infection. CRP is routinely used as a non-specific marker of inflammation and is to be distinguished from high-sensitivity CRP (hsCRP) which is used as a marker of increased risk for cardiac diseases. CRP does not normally increase significantly in mild viral respiratory infections. However, significant increases of CRP have been reported in COVID-19 patients. Procalcitonin (PCT) is a marker of disorders that are accompanied by systemic inflammation and sepsis. Serial PCT measurement in patients with or without severe COVID-19 may play a role for predicting evolution towards a more severe form of disease. D-dimer values are frequently increased in patients with COVID-19, being variably observed in 36–43% of positive cases, and are considerably higher in COVID-19

patients with severe disease than in those without the disease. Elevated D-dimer in patients with severe COVID-19 is associated with worse clinical outcomes, and very elevated values may indicate subclinical thrombosis, or risk for thrombosis, with need for anti-thrombotic therapy. Finally, Interleukin-6 (IL-6) is a cytokine produced by cells of the immune system in response to an infection. A low level of IL-6 may be expected for most patients with a less severe inflammatory response. Very elevated IL-6 can result in a severe inflammatory response and thus a high level of IL-6 may be an indication that the inflammation is severe and could lead to complications, and may play a role in early aggressive therapy and ventilation of patients.

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