May 7, 2020 COVID-19 Update

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**Contents include:**

Extended summary:

- Multicenter Pediatric CICU Webinar re: Kawasaki-like illness in pediatric COVID-19

Brief summaries:

- Multicenter Pediatric CICU Webinar re: Kawasaki-like illness in pediatric COVID-19
- Suggested potential triage/evaluation/management plan
- Paediatric Intensive Care Society Alert re: Novel Presentation of Multisystem Inflammatory Disease
- NYC Health Alert: Pediatric Multisystem Inflammatory Syndrome Potentially Associated with COVID-19
- ACC Key Questions on COVID-19 and Cardiovascular Disease

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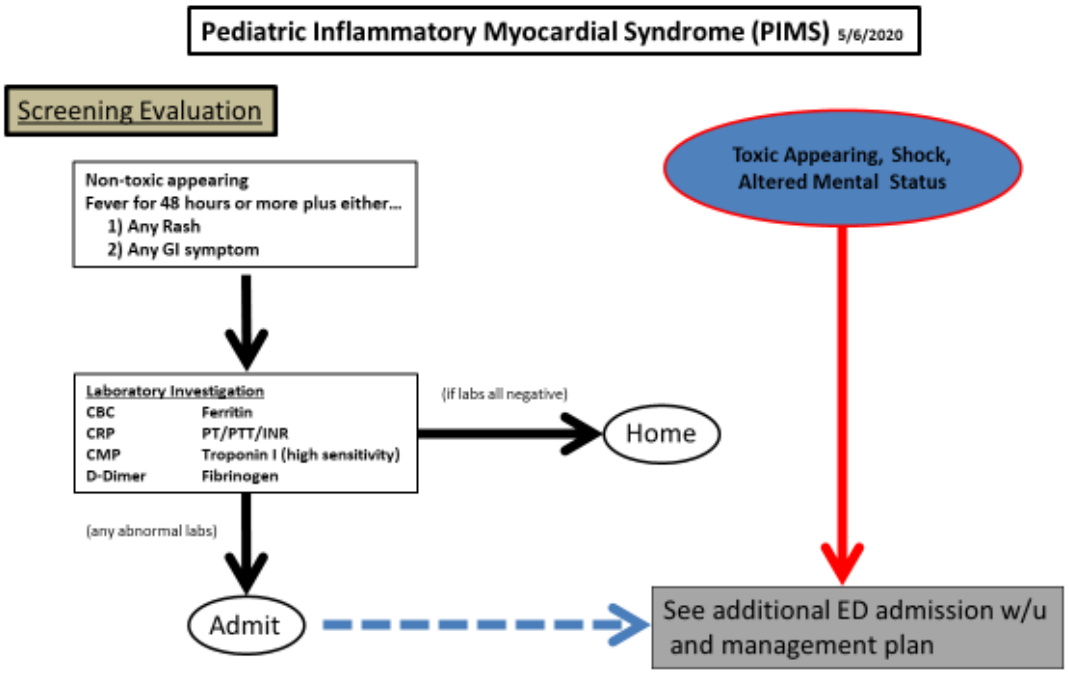
<u>Multicenter Pediatric CICU Webinar re: Kawasaki-like illness in pediatric COVID-19 (May 2 and May 5)</u>

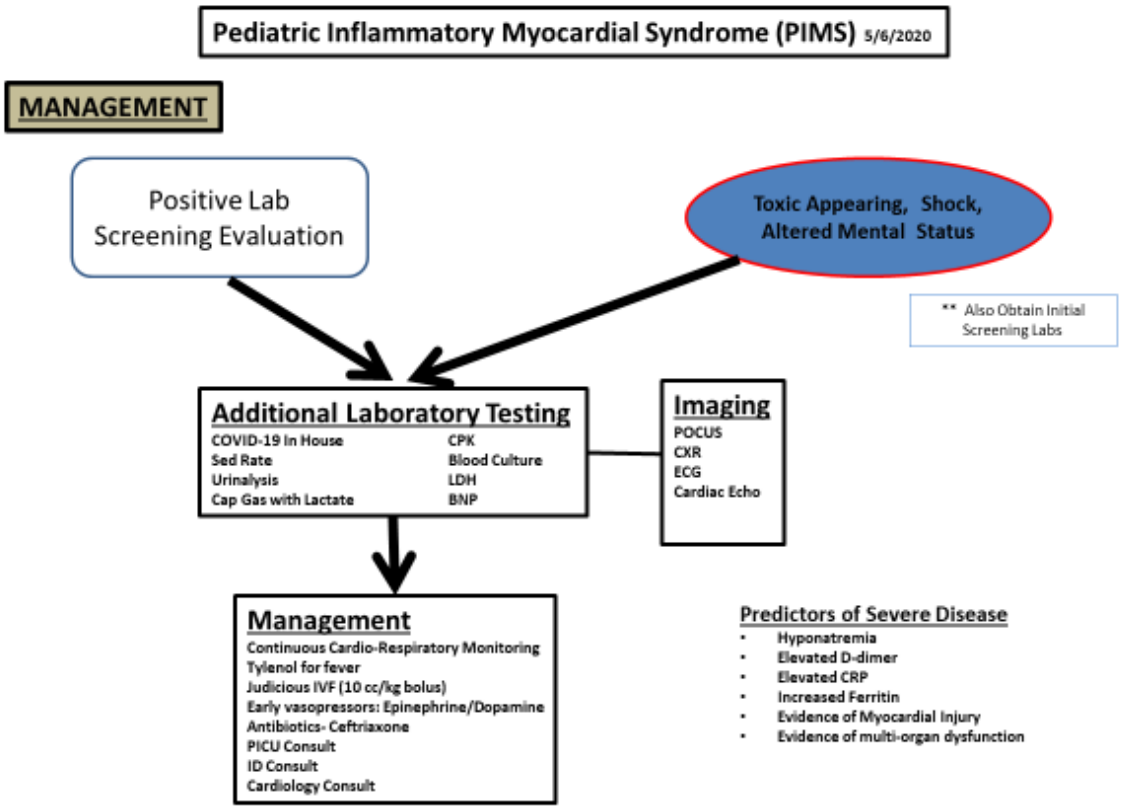
- Several large international pediatric centers have found that a group of pediatric patients with COVID-19 develop systemic multisystem disease, with evidence of severe inflammation – similar presentation also seen in COVID-19 negative patients
- Syndrome has overlap with: Kawasaki Disease/Kawasaki Shock Syndrome, Toxic Shock Syndrome, HLH/macrophage activation syndrome, vasculitis
    - Differential diagnosis includes: typical KD happening now, TSS from bacterial source, myocarditis, etc
- Webinar format: Case-series from multiple international centers followed by discussion with KD and other experts
    - UK, Spain, Italy, France
- Proposed names for syndrome:
    - COVID-19-associated hyperinflammatory response syndrome
    - Multi-system inflammatory syndrome due to COVID-19
    - Corona shock syndrome
- No reported deaths
- Demographics: older than KD
    - Average age 9 in UK (vs 2.5 in USCD KD registry) with cases up to age 17
    - Higher percentage of Black patients than in UK population (40% vs 14%)
    - Very few Asian patients – on asking Japan, Taiwan, Korea, no cases reported
    - Majority are previously healthy
    - Peak of cases seems to be ~1mo after COVID peak
- Clinical presentation: **knowing that this is the selected group who required ICU care**
    - Vast majority have fever
    - Vast majority have shock requiring vasoactive support
        - 10-40% required ECMO at different centers
    - Majority have significant abdominal/GI symptoms
        - Some so significant that ex-lap performed
    - Many have AKI, but few required renal replacement therapy
    - Less than half have respiratory symptoms
    - Rash – variable, with some series majority and some as low as 1/3
    - Conjunctivititis/mucus membrane involvement, cracked lips – occasional
- Cardiovascular considerations:
    - Profound vasoplegia – can happen very quickly
    - Majority with ventricular dysfunction, with most mild-moderate
    - Many with pericardial effusions, although no reported cases of tamponade
    - High arrhythmia burden with several cases of cardiac arrest due to VT/VF
    - Many questions about degree of coronary involvement
        - Royal Brompton: 5/37 cases had coronary involvement
        - France: one 16y with giant aneurysms

- Lab findings: comparing cases to UCSF KD database, lab findings are markedly different than KD or KD shock
    - COVID+ in 2/3 or more: some PCR+, some Ab+ only
    - Troponin mild to moderately elevated -> high
    - BNP often very high
    - IL-6 extremely high when checked
    - Markedly elevated WBC with lymphopenia
    - Markedly elevated ESR/CRP, D-dimer, ferritin
    - Platelets often normal or low
- Management: no consensus at this time, but multiple different strategies were discussed and include
    - Supportive
        - Most need pressors – norepinephrine, epinephrine, levosimendan were mentioned, but specific strategies weren't addressed in detail; specifically milrinone was not discussed
        - Many need intubation
        - Some need ECMO
            - Consideration for targeting higher anti-Xa levels due to prothromobotic state
        - Aspirin, anticoagulation in general – no consensus, but given concern for microvascular thrombosis as an etiology/pathophysiologic contributor, some centers are therapeutically anticoagulating
    - Immunomodulation
        - IVIg/steroids when presentation more Kawasaki-like or for coronary involvement, but recommended discussing with ID/rheumatology and ensuring appropriate labs prior to IVIg
        - IL-1, IL-6 blockade
- Possible pathophysiology/mechanism: likely an abnormal/exaggerated immune complex/Ig response to SARS-CoV-2
    - Based on timing of peak and plurality of patients who are COVID PCR negative, seems to be delayed immune response and NOT an acute infection with COVID-19
        - From SARS, we know Ab against the spike protein activated macrophages and enhanced inflammatory components of disease
    - ?T cell mediated: after recognizing virus and/or self-antigens, failure to deactivate macrophage activation
    - Genetics likely play a role in susceptibility (similar to KD)
        - B cell regulation, class switching, Ig clearance through FCGR2
- Key action item: Continued collaboration between centers to collect and analyze cases
    - Data: demographics, pre-treatment labs (COVID PCR/Ab, fibrinogen, CRP, D-dimer, ferritin, troponin, BNP, cytokine panel, sIL-2-receptor, IL-6, CBC, coags, LFTs
    - Err on the side of including too many patients
    - Utilize existing databases if possible
- Practical application:
    - Be aware that children presenting with GI symptoms and/or skin findings may develop marked cardiogenic and/or distributive shock requiring inotropic support
    - At this time, insufficient data to support echo for all children with COVID (which would go against the recent ASE statement)
    - Consider collecting the above labs for trending through the course of illness on patients admitted with syndrome
    - Monitor closely for arrhythmias
    - Echo all patients with shock and concern for this syndrome with particular attention to the coronaries
    - Early cardiology follow up for patents with any cardiac involvement (ventricular dysfunction, coronary changes)
        - Royal Thames – one month follow up with echo for any patients with overall syndrome regardless of inpatient cardiac involvement
        - For coronary involvement – consider KD-like follow up pathway

Suggested potential triage/evaluation/management plan courtesy of Children's Hospital of Michigan (DMC) for MDHHS Region 2 South Healthcare Coalition




Pediatric Inflammatory Myocardial Syndrome (PIMS)



Paediatric Intensive Care Society Alert re: Novel Presentation of Multisystem Inflammatory Disease

- While in general there have been very few cases of children becoming severely ill from COVID-19, several critically ill children have presented with clinical syndrome on the spectrum of Kawasaki and Toxic Shock Syndrome overlap with lab evidence of severe COVID-19
- Abdominal pain and GI sx as well as evidence of cardiac inflammation are key findings – some have coronary artery changes
- Lab features have features of cytokine storm, hyperinflammation, macrophage activation syndrome, HLH
- Children with concerning cases/symptoms should be discussed with ID and cardiology early

NYC Health Alert: Pediatric Multisystem Inflammatory Syndrome Potentially Associated with COVID-19

- Fifteen children aged 2-15y in NYC have multi-system inflammatory syndrome
- Some features of Kawasaki disease, some features of toxic shock syndrome
- All have fever and markedly elevated inflammatory markers
- Most have abdominal pain and rash, but less than half had respiratory symptoms
- Some have COVID PCR+, some only COVID Ab+, few with all COVID testing negative
- Request to report all patients <21 with 4+ days fever, incomplete or typical KD and/or TSS presentation regardless of COVID testing results

ACC Key Questions on COVID-19 and Cardiovascular Disease

- Concise summary of ACC clinical guidelines related to cardiac care during COVID-19
- Discussed lab testing, imaging, medications considerations, and other topics for caring for cardiac complications of COVID-19 as well as management of patients with underlying cardiovascular disease with and without COVID-19 in the current era