May 7, 2020 COVID-19 Update

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

- 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
  - Conjunctivitis/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
  o COVID+ in 2/3 or more: some PCR+, some Ab+ only
  o Troponin mild to moderately elevated -> high
  o BNP often very high
  o IL-6 extremely high when checked
  o Markedly elevated WBC with lymphopenia
  o Markedly elevated ESR/CRP, D-dimer, ferritin
  o Platelets often normal or low
• Management: no consensus at this time, but multiple different strategies were discussed and include
  o 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 prothrombotic state
    ▪ Aspirin, anticoagulation in general – no consensus, but given concern for microvascular thrombosis as an
      etiology/pathophysiologic contributor, some centers are therapeutically anticoagulating
  o 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
  o 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
  o ??T cell mediated: after recognizing virus and/or self-antigens, failure to deactivate macrophage activation
  o 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
  o 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
  o Err on the side of including too many patients
  o Utilize existing databases if possible
• Practical application:
  o Be aware that children presenting with GI symptoms and/or skin findings may develop marked cardiogenic and/or
    distributive shock requiring inotropic support
  o At this time, insufficient data to support echo for all children with COVID (which would go against the recent ASE
    statement)
  o Consider collecting the above labs for trending through the course of illness on patients admitted with syndrome
  o Monitor closely for arrhythmias
  o Echo all patients with shock and concern for this syndrome with particular attention to the coronaries
  o Early cardiology follow up for patients 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) 5/6/2020

Screening Evaluation

Non-toxic appearing
Fever for 48 hours or more plus either...
1) Any rash
2) Any GI symptom

Laboratory Investigation
- CBC
- Ferritin
- CRP
- PT/PTI/INR
- Troponin I (high sensitivity)
- D-Dimer
- Fibrinogen

(if labs all negative)

Admit

Toxic Appearing, Shock, Altered Mental Status

See additional ED admission w/u and management plan

Pediatric Inflammatory Myocardial Syndrome (PIMS)

MANAGEMENT

Positive Lab Screening Evaluation

Additional Laboratory Testing
- COVID-19 in House
- Sed Rate
- Urtasalysis
- Cap. Gas with Lactate
- CPK
- Blood Culture
- LDH
- BNP

Imaging
- POCUS
- CXR
- EKG
- Cardiac echo

Management
- Continuous Cardio-Respiratory Monitoring
- Tylenol for fever
- Judicious IVF (10 cc/kg bolus)
- Early vasopressors: Epinephrine/Dopamine
- Antibiotics: Ceftriaxone
- PICU Consult
- ID Consult
- Cardiology Consult

Predictors of Severe Disease
- Hypotension
- Elevated D-dimer
- Elevated CRP
- Increased Ferritin
- Evidence of Myocardial Injury
- Evidence of multi-organ dysfunction

** Also Obtain Initial Screening Labs
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