Pediatric Multi-system Inflammatory Syndrome (PMIS) Temporally Associated with COVID-19
Hasbro Children's Hospital – Clinical Guideline
Last updated May 14, 2020

This clinical guideline is a working, iterative document given the nature of this new clinical syndrome, with growing evidence and experience. The guideline will be updated as recommendations evolve.

Description of patients

- Likely pediatric/young adult patients (wide age range, with average age 8-11 years old)
- Signs and symptoms are consistent with post-infectious immune response/cytokine storm syndromes
- Often exposure to COVID (family member positive or with fever/respiratory symptoms, mild or no symptoms for the patient) but not always known
- Often 2-3 weeks (or more) post exposure or mild symptoms
- As above, similarities with many immune response syndromes such as Kawasaki Disease with shock, cytokine release syndrome after CAR-T therapy, HLH, MAS
- Presenting with or can rapidly progress to shock, often cardiogenic
- Some male predominance
- Some degree of obesity prevalence
- Excludes patients with typical Kawasaki Disease, other etiologies of shock such as TSSS, gram negative bacteremia, and others

Presenting signs and symptoms

- Fever refractory to anti-pyretics
- GI symptoms/diarrhea
- Rash (can be desquamating)
- Neurologic symptoms/altered mental status
- Tachycardia
- Hypotension
- Poor perfusion
- Hypoxia

Common laboratory findings

- Elevated D-dimer
- Elevated ferritin
- Elevated CRP/ESR
- Elevated troponin
- Elevated BNP
- Lymphopenia, sometimes with neutrophilia
- Hyponatremia
- Almost always COVID-19 PCR negative, often COVID-19 IgG/IgM antibody positive

Signs and symptoms to consider referral/transfer to Emergency Department

Clinical suspicion and history consistent with syndrome, with special attention to:

- Tachycardia (with or without fever)
- Refractory fever
- Altered mental status
- Hypotension

- Decreased urine output
- Hypoxia

Suggested initial hospital workup/evaluation

Laboratory tests	**Imaging/Other diagnostics**	**Consultations**
CBC with differential Blood culture Blood gas with lactate Ferritin Fibrinogen D-dimer PT/INR PTT TEG (thromboelastography) Triglycerides CRP Troponin BNP CK-MB CMP/M/P LDH COVID-19 PCR COVID-19 IgM/IgG RPP Urinanalysis Type and screen If possible: • IL-6 • Soluble IL-2 receptor • IL-1	CXR 12 lead EKG Echo (timing in conjunction with Cardiology consultation, and with clinical consideration of phenotype)	Cardiology Infectious Disease Rheumatology Hematology/Oncology Surgery if ECMO is being considered

Clinical decision-making regarding admission status

- Patients with suspicion for PMIS should be admitted given the small amount of clinical experience with this new presentation as well as reports of rapid decline
- Patients who are hemodynamically stable may be admitted to wards with cardiorespiratory monitoring and frequent clinical re-assessment
- Patients with persistent tachycardia, any worsening perfusion, or other metrics of declining cardiac output should be evaluated by the FAST Team with low threshold for immediate transfer to PICU

Therapies and interventions

- If hypotensive, consider appropriate early inotropic support (often vasoplegia/warm shock with benefit from norepinephrine) prior to third fluid bolus, or earlier in patients who appear adequately hydrated
- Echocardiogram can guide fluid resuscitation management by identifying possible myocardial dysfunction and assessing preload

- Consider fluid management carefully as respiratory failure in patients has tended to occur after significant fluid resuscitation
- Early consideration of the need for central access
- Empiric antibiotics for sepsis
- Initiate thromboprophylaxis as per Pediatric COVID-19 Thromboprophylaxis guideline and in consultation with Pediatric Hematology/Oncology
- Kawasaki-predominant phenotype: initiate IVIG (may require up to 2 doses; 2 g/kg/dose) and then consider anakinra
- Cytokine release syndrome predominant phenotype: initiate anakinra, and then consider IVIG. May also consider tocilizumab with elevated IL-6 with consideration of drug availability.
- Consider initiating steroids in conversation with consultants (steroids may be a component of ARDS management or refractory shock management as well)
- Standing anti-pyretics
- Discuss ECMO early for refractory cardiogenic shock

Diagnostic monitoring

- Serial echocardiograms as clinically indicated
- Trend CBC, troponin, BNP, ferritin, fibrinogen, PT/INR, PTT, d-dimer as clinically indicated and in conjunction with consultant guidance

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