Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

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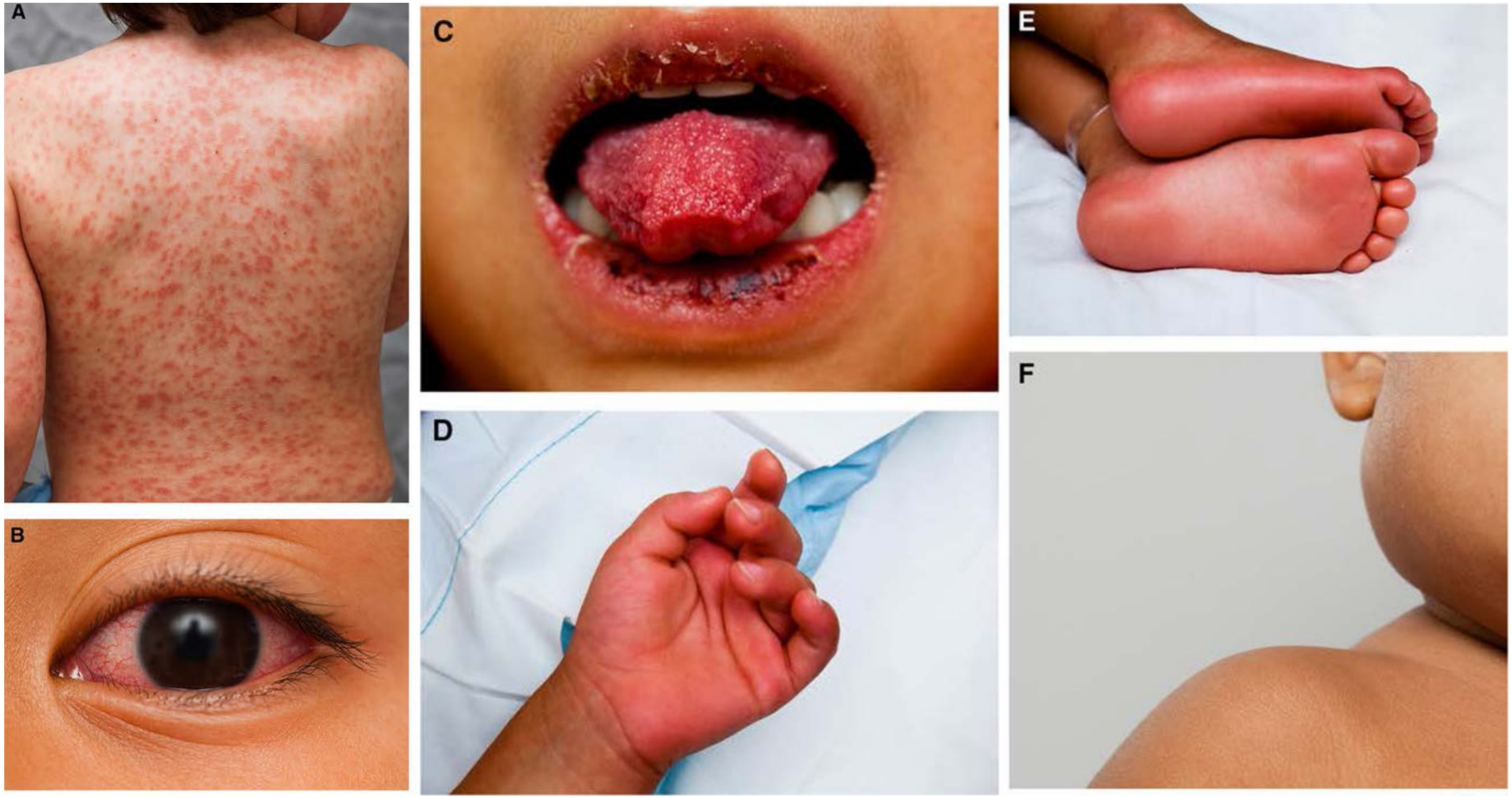
Kawasaki Disease

- Kawasaki disease is an acute vasculitis of childhood that leads to coronary artery aneurysms in ≈25% of untreated cases. It has been reported worldwide and is the leading cause of acquired heart disease in children in developed countries.

- Self-limited febrile illness of unknown cause that predominantly affects children <5 years of age.

- Features: Manifestations include 5 or more days of fever (usually high fever), together with extremity changes, rash, conjunctivitis, oral changes, and unilateral cervical lymphadenopathy. There are also certain lab markers that are used in diagnosis (CBC, ESR, CRP, UA)
- Typically requires hospitalization for administration of IVIG, ASA, baseline echocardiogram (typically normal), and outpatient follow up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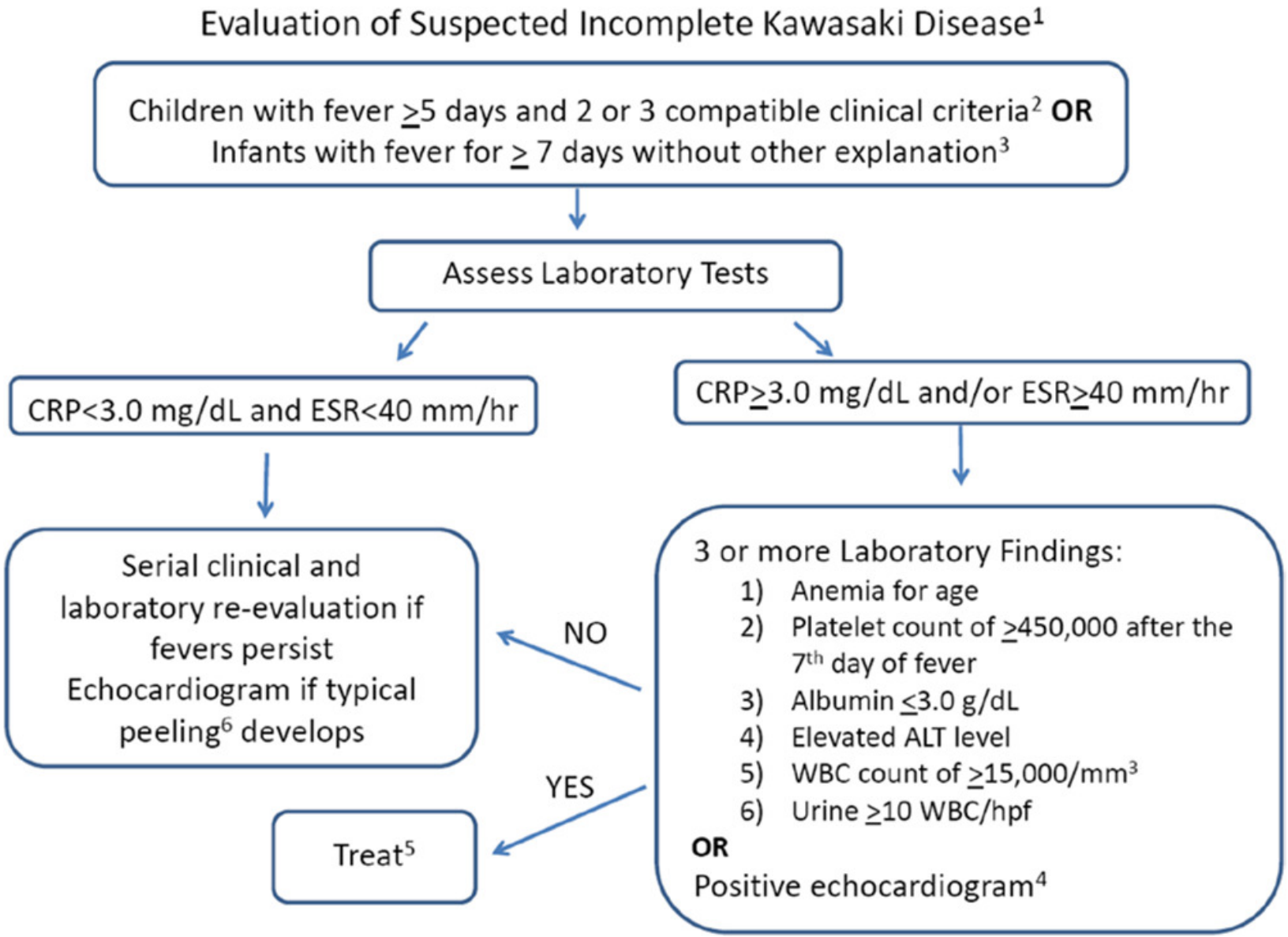

Evaluation of Suspected Incomplete Kawasaki Disease[1]
Children with fever ≥5 days and 2 or 3 compatible clinical criteria[2] OR
Infants with fever for ≥ 7 days without other explanation[3]
Assess Laboratory Tests
CRP<3.0 mg/dL and ESR<40 mm/hr
CRP≥3.0 mg/dL and/or ESR≥40 mm/hr
Serial clinical and laboratory re-evaluation if fevers persist
Echocardiogram if typical peeling[6] develops
NO
YES
Treat[5]
3 or more Laboratory Findings:
1) Anemia for age
2) Platelet count of ≥450,000 after the 7th day of fever
3) Albumin ≤3.0 g/dL
4) Elevated ALT level
5) WBC count of ≥15,000/mm3
6) Urine ≥10 WBC/hpf
OR
Positive echocardiogram[4]

Kawasaki Disease

- Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease, McCrindle et al, 2017 (American Heart Association)
  - Google search: *Kawasaki McCrindle*

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

- **COVID**:

- CDC: Clinician Outreach and Communication Activity (COCA) Call

- https://emergency.cdc.gov/coca/calls/index.asp
  - **Google search: *cdc coca***

  - ***Also:* UpToDate**

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

- Noticed in UK and US in March. UK ~40 cases, NY ~30 cases.
- Some - typical Kawasaki disease features, but some distinct differences
- Common features: severity of illness, prolonged fever, **GI symptoms** (in particular diarrhea), sore throat headache, rash, conjunctivitis, some with shock, multi-organ system dysfunction, evidence of cardiac dysfunction, some common lab findings
- UK: only 37% respiratory symptoms

CDC Definition

- Age <21 years
- A presentation consistent with MIS-C, including **all** of the following:
  - Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
  - Laboratory evidence of inflammation (eg, elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin-6 [IL-6] level; neutrophilia; lymphocytopenia; and/or hypoalbuminemia)
  - Severe illness requiring hospitalization
  - ≥2 organ systems involved (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, and/or neurologic)
- No alternative plausible diagnoses
- Recent or current SARS-CoV-2 infection or exposure, defined as **any** of the following:
  - Positive SARS-CoV-2 polymerase chain reaction (PCR)
  - Positive serology for SARS-CoV-2
  - Positive antigen test
  - COVID-19 exposure within the four weeks prior to the onset of symptoms

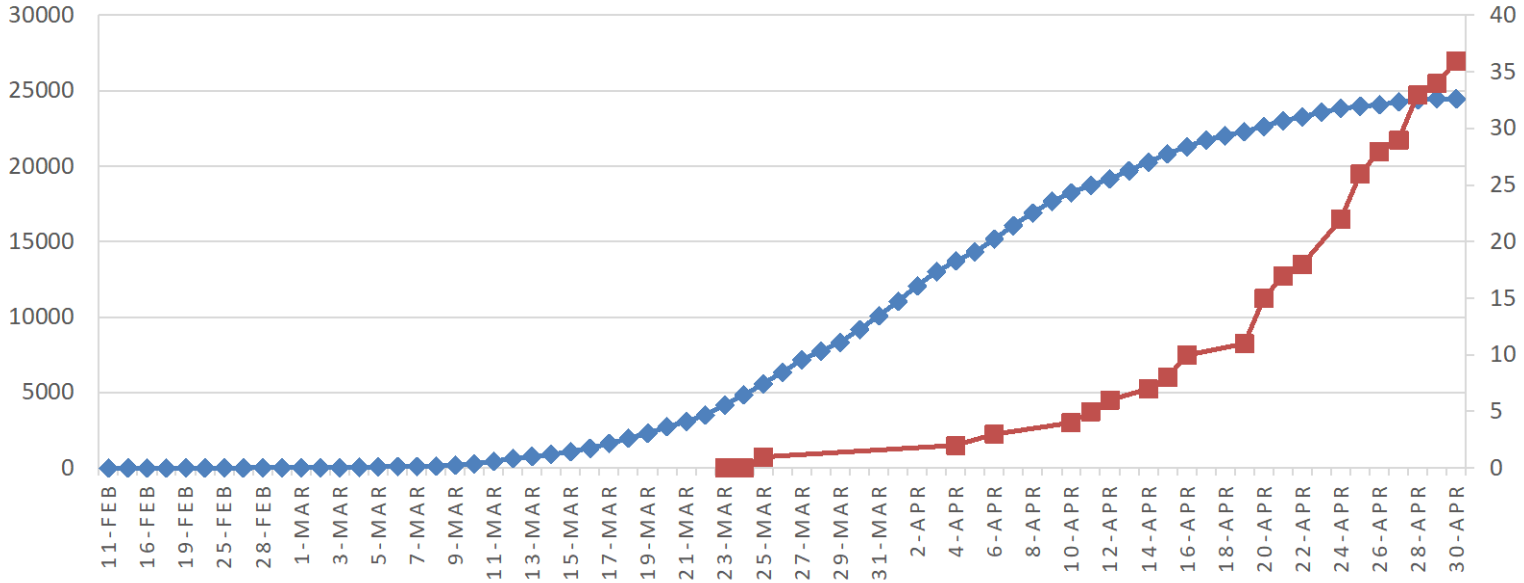
WHO Definition

- Age 0 to 19 years old, **and**
- Fever for ≥3 days, **and**
- Elevated markers of inflammation (eg, erythrocyte sedimentation rate, C-reactive protein, or procalcitonin), **and**
- No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal shock syndromes, **and**
- Evidence of SARS-CoV-2 infection (positive reverse transcription PCR [RT-PCR], antigen test, or serology) or contact with an individual with COVID-19, **and**
- Clinical signs of multisystem involvement (at least **two** of the following):
  - Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
  - Hypotension or shock
  - Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/brain natriuretic peptide [BNP])
  - Evidence of coagulopathy (prolonged prothrombin time or partial thromboplastin time; elevated D-dimer)
  - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

PIMS-TS appear to be a month behind the COVID19 peak in the population

Public Health England

Laboratory Confirmed COVID-19 cases, London



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- **AGE: 1-17 years old, median 8-11 years of age**
- Ethnicity: AA vs Asians

- NY: No underlying medical conditions (excluding obesity): 79%
- Normal weight: 45%; Obese: 39%
- Reactive airway disease: 15%

- Labs: Lymphopenia (80%), Neutrophilia, Anemia, Raised D-dimer, Raised Troponin, Raised CRP (206), Raised BNP (3325)
- CXR/CT chest/Abdominal US or CT: may have abnormal findings but may be normal

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

- Fever duration prior to presentation: 4 dy
- Neurocognitive sx's: 58%
- GI sx's: 97%
- Respiratory sx's: 52%
- Shock: 76%
- Complete Kawasaki disease criteria: 64%
- With shock: 76%

- Acute liver injury: 21%
- AKI: 70%
- O2 or Positive Pressure: 52%
- Mechanical ventilation: 18%
- Intubation days: 3

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Cardiac Findings:

- Any coronary artery abnormalities: 48%
- Any myocardial dysfunction: 58%
- Mild: 33%
- Moderate: 24%
- Severe: 0%

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- **<u>Medications</u>**:

- IVIG: 100%
    - 2nd dose: 30%
- Methylprednisolone: 70% • Aspirin: 88%
- Anakinra: 12%
- Tocilizumab: 9%
- Infliximab: 3%
- Enoxaparin: 42%

Up To Date

	Frequency (%)
Presenting symptoms	
▪ Persistent fevers (median duration 4 days)	100
▪ Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)	60 to 97
▪ Rash	50 to 60
▪ Neurocognitive symptoms (headache, lethargy, confusion)	30 to 58
▪ Respiratory symptoms (tachypnea, labored breathing)	32 to 65
▪ Conjunctivitis	32
▪ Mucous membrane involvement	19
▪ Sore throat	14
▪ Swollen hands/feet	8
Clinical findings	
▪ Shock	60 to 80
▪ Criteria for complete Kawasaki disease met	50 to 64
▪ Myocardial dysfunction (by echocardiogram or elevated troponin/BNP)	50 to 100
▪ Acute respiratory failure requiring noninvasive or invasive ventilation	52 to 68
▪ Acute kidney injury	38 to 70
▪ Serositis (small pleural, pericardial, and ascitic effusions)	24 to 50
▪ Acute hepatic failure	21

Up To Date

Laboratory findings	
▪ Abnormal blood cell counts	
• Lymphocytopenia	80 to 95
• Neutrophilia	80 to 90
• Mild anemia	70
• Thrombocytopenia	30 to 80
▪ Elevated inflammatory markers	
• C-reactive protein	90 to 95
• Erythrocyte sedimentation rate	80
• D-dimer	80 to 95
• Fibrinogen	90
• Ferritin	75
• Procalcitonin	ND
• Interleukin-6	ND
▪ Elevated cardiac markers	
• Troponin	60 to 90
• BNP or NT-pro-BNP	90 to 100
▪ Hypoalbuminemia	73
▪ Mildly elevated liver enzymes	70
▪ Elevated lactate dehydrogenase	50 to 60
▪ Hypertriglyceridemia	70

Up To Date

Imaging findings	
▪ Echocardiogram	
• Depressed LV function	50 to 60
• Coronary artery dilation/aneurysm	20 to 50
• Other findings can include mitral regurgitation and pericardial effusion	--
▪ Chest radiograph	
• Normal in many patients	--
• Abnormal findings included small pleural effusions, patchy consolidations, focal consolidation, and atelectasis	--
▪ Chest CT	
• Findings generally similar to those on chest radiograph	--
• A few patients had nodular ground-glass opacification	--
▪ Abdominal imaging (ultrasound and/or CT)	
• Findings are nonspecific, including free fluid, ascites, bowel and mesenteric inflammation, including terminal ileitis, mesenteric adenopathy/adenitis, and pericholecystic edema	--

Hypoxia

"Epidemiological Characteristics of 2,143 Pediatric Patients With 2019 Coronavirus Disease in China," Pediatrics, pre-publication release

- moderate disease with pneumonia, cough, "no obvious hypoxia such as shortness of breath"

- severe disease: Oxygen Saturations <92%

-"COVID-19 in Children: Initial Characterization of the Pediatric Disease" April

- **Among children who were symptomatic, 5% had dyspnea or hypoxemia (a substantially lower percentage than what has been reported for adults), and 0.6% progressed to acute respiratory distress syndrome or multiorgan system dysfunction (a rate that is also lower than that seen in adults).** Preschool-aged children and infants were more likely than older children to have severe clinical manifestations.
- - No "inflamm" or "kawa" in paper
- - UpToDate: no "hypox" "saturation" "oximet"

My personal takeaway points

- Rare
- Age distribution very different than Kawasaki
- May not have respiratory symptoms
- NY: PCR test x 2 separated by 12 hours for suspected patients given high false negative rates

If you have a sick child

Test for COVID antigen and Ab

CBC, CMP, **CRP, BNP, Troponin**

Consider: **ECG**, Ferritin, d-dimer, lactate dehydrogenase, procalcitonin, coags

- Appropriate level of care AND **call cardiology**

My personal takeaway points

- **Possibly sick child:**
- Prolonged fever, GI complaints, Kawasaki features, unusual tachycardia (concerns for myocarditis)

- Test for COVID antigen and Ab
- CBC, CMP, **CRP, BNP, Troponin**
- **Close follow up

- * may be something else: bacterial sepsis, Kawasaki Disease, Toxic Shock, Appendicitis, SLE, Hemophagocytic lymphohistiocytosis (HLH). Consider Viral respiratory panels, blood cultures, etc

Resources

- **Kawasaki**: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease, McCrindle et al, 2017 (American Heart Association)
  - Google search: *Kawasaki McCrindle*
- **COVID**: https://emergency.cdc.gov/coca/calls/index.asp
  - Google search: *cdc coca*

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