KEY FACTS

TERMINOLOGY

- COVID-19: Acute infection with SARS-CoV2
- MIS-C: Condition characterized by fever, inflammation, & multiorgan dysfunction that has temporal association with SARS-CoV-2 infection

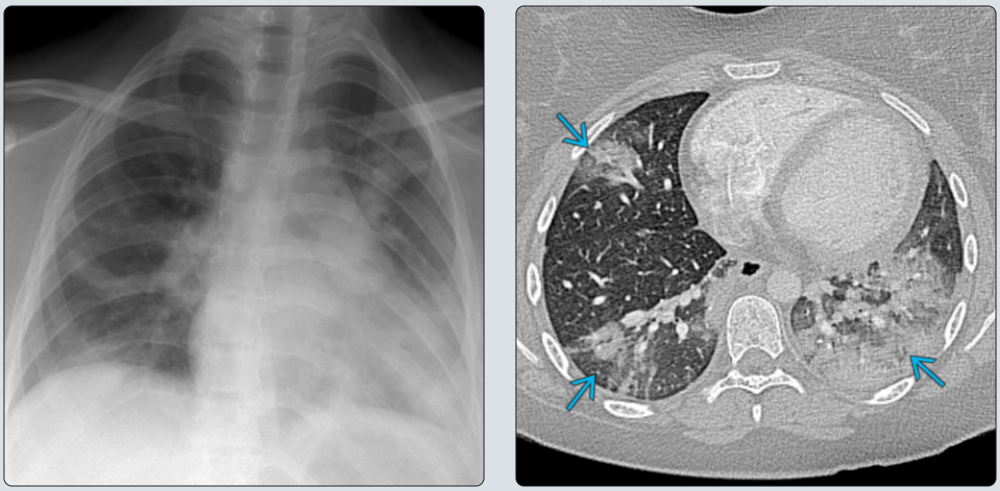
IMAGING

- COVID-19
  - Chest: Bilateral or unilateral peripheral subpleural &/or peribronchial lower lobe-predominant ground-glass opacities (GGO) ± consolidation, bronchial wall thickening, halo sign
    - Uncommon features: Nodules, cavitation, pleural effusions
  - Neuro: ADEM-like imaging pattern, myelitis, neuritis, cerebrovascular complications
- MIS-C
  - Cardiac in 86.5%: Left ventricular (LV) dysfunction, shock, myocarditis, coronary artery dilatation/aneurysm
  - GI: Ascites, RLQ inflammation, bowel wall thickening, pancreatitis, hepatomegaly, splenomegaly, gallbladder sludge, pericholecystic fluid, lymphadenopathy
  - Chest: Pulmonary edema, pleural effusions, ground-glass opacities (GGO) related to ARDS, pulmonary embolism
  - Neuro: ↑ T2 signal lesions + restricted diffusion in corpus callosum, restricted diffusion in thalami, focal cerebral arteriopathy, ADEM-like findings, myelitis, neuritis, cerebrovascular complications, myositis of face & neck

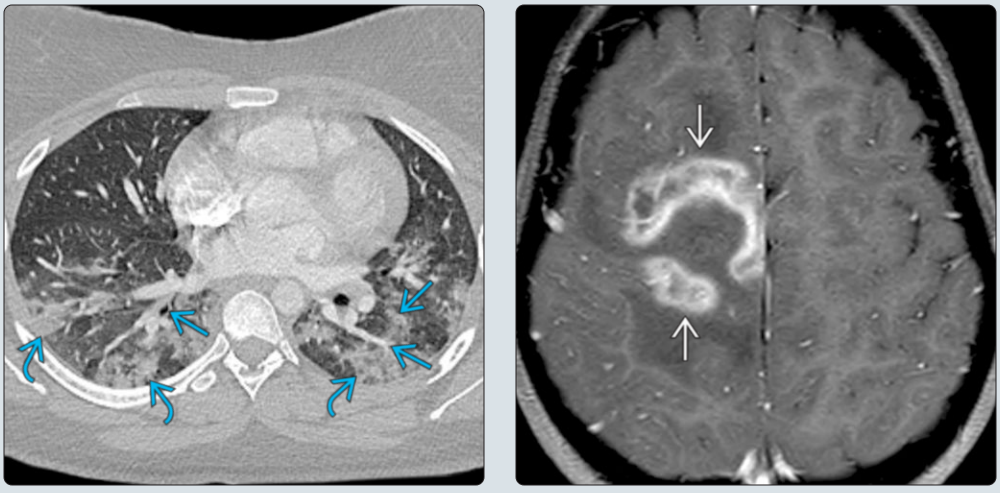
CLINICAL ISSUES

- COVID-19
  - Overall less severe disease in children: ~ 1.5 % of hospitalizations & 0.3% of deaths are related to COVID-19 in USA
- MIS-C
  - > 60% require ICU & vasopressors, mortality 1.8%
  - LV ejection fraction normalizes in most 1-2 weeks after presentation

(Left) *Frontal radiograph in a 14-year-old patient with shortness of breath & fever demonstrates hazy & patchy bilateral pulmonary opacities.* **(Right)** *Axial CECT in the same patient shows bilateral lower lung zone-predominant ground-glass & consolidative densities. The patient tested positive for COVID-19 on nasopharyngeal RT-PCR. Other features seen in pediatric cases of COVID-19 include bronchial wall thickening & the halo sign (not shown).*



(Left) *Axial CECT from a 17 year old demonstrates bilateral symmetric lower lung zone-predominant ground-glass & patchy densities. Bronchial wall thickening is also noted.* **(Right)** *Axial T1 C+ FS MR in 9 year old with left-sided weakness shows a right cerebral lesion with cortical enhancement & hemorrhagic necrosis (confirmed on T2 & SWI with minimal precontrast T1 shortening) due to COVID-19-associated vasculitis & infarction.*



TERMINOLOGY

Definitions

- COVID-19: Severe acute respiratory syndrome caused by SARS-CoV-2 virus
- Multisystem inflammatory syndrome in children (MIS-C): Condition characterized by fever, inflammation, & multiorgan dysfunction that has temporal association with SARS-CoV-2 infection

IMAGING

Radiographic Findings

- COVID-19
  - Bilateral or unilateral peripheral lower lobe-predominant patchy consolidation & ground-glass opacities (GGO)
- MIS-C
  - Cardiomegaly, pulmonary edema, pleural effusions, acute respiratory distress syndrome (ARDS)

CT Findings

- COVID-19
  - Bilateral or unilateral peripheral subpleural &/or peribronchial lower lobe-predominant GGO ± consolidation
  - Bronchial wall thickening (more common in children compared to adults)
  - Halo sign: Round consolidative opacity with rim of GGO
  - Uncommon: Pulmonary nodules, pleural effusions, cavitation, lymphadenopathy
- MIS-C
  - Chest: Pulmonary edema, pleural effusions, GGO related to ARDS, pulmonary embolism, lower lobe opacities
  - Cardiac: Cardiomegaly, coronary artery ectasia/aneurysm, pericardial effusion
  - Gastrointestinal (GI): Ascites, right lower quadrant (RLQ) inflammation, bowel wall thickening, pancreatitis, hepatomegaly, splenomegaly, gallbladder sludge &/or wall thickening, pericholecystic fluid, lymphadenopathy

MR Findings

- COVID-19
  - Neurologic
    - Acute disseminated encephalomyelitis (ADEM)-like imaging pattern: Patchy ↑ T2 involving gray & white matter ± enhancement or diffusion restriction
    - Myelitis: Long-segment central cord ↑ T2
      - Rarely can rapidly progress to acute necrotizing myelitis with cord edema, enhancement, diffusion restriction, & hemorrhage
    - Neuritis: Enhancement of cranial/spinal nerves
- MIS-C
  - Cardiac
    - ↓ left ventricle ejection fraction (LVEF)
    - Valvular dysfunction
    - Myocarditis: Myocardial edema with ↑ T2 signal globally or at basal septal segments
  - Neurologic
    - Encephalopathy: ↑ T2 ± restricted diffusion in corpus callosum (splenium + genu), restricted diffusion in bilateral lateral thalamic nuclei
    - Focal cerebral arteriopathy: Cerebral artery stenosis, wall thickening, & concentric contrast enhancement
    - Susceptibility-induced signal drop-out due to parenchymal microthrombi
    - Myositis of neck & face musculature
    - ADEM-like imaging pattern, myelitis, neuritis

Ultrasonographic Findings

- COVID-19
  - Lung findings: Pleural irregularity, vertical artifact, confluent B-lines, subpleural consolidation
- MIS-C
  - Echocardiography: Coronary artery ectasia/aneurysm, ↓ LVEF, LV diastolic dysfunction, ↑ echogenicity of interventricular septum & pericardium, valve dysfunction
  - GI: Ascites, RLQ inflammation, bowel wall thickening, pancreatitis, hepatomegaly, splenomegaly, gallbladder sludge, pericholecystic fluid, lymphadenopathy
  - Genitourinary: Echogenic kidneys

Imaging Recommendations

- COVID-19
  - Imaging is not indicated for screening or for known or suspected COVID-19 with mild disease without risk factors for progression
  - Chest radiograph is appropriate for initial imaging for pediatric patients with moderate-to-severe known/suspected COVID-19
  - Chest radiograph & CT can be considered for pediatric patients with known/suspected COVID-19 & worsening disease or lack of response to therapy
- American College of Rheumatology Clinical Guidance for Pediatric Patients with MIS-C
  - Imaging of chest, abdomen, &/or CNS as needed
  - Echocardiogram at diagnosis & during clinical follow-up & repeated at minimum of 7-14 days & 4-6 weeks after presentation; LV dysfunction & coronary artery aneurysm will require more frequent follow-up
  - Cardiac MR may be indicated 2-6 months after MIS-C diagnosis with significant transient LV dysfunction
  - Cardiac CT if suspicion of distal coronary artery aneurysm not well seen on echocardiogram

DIFFERENTIAL DIAGNOSIS

COVID-19

- **Other infectious pneumonias**
  - Bacterial: Typically focal, single segment or lobe
  - Fungal: Nodules, cavitation, air crescent sign
  - Viral (influenza): Centrilobular nodules
- **E-cigarette vaping-associated lung injury (EVALI)**
  - Subpleural sparing
  - Centrilobular nodules & GGO
  - Atoll sign
- **ADEM**
  - Similar imaging but may not meet clinical definition

Multisystem Inflammatory Syndrome in Children

- **Kawasaki disease (KD)**
  - More common ≤ 5 years old
  - LV dysfunction & shock are less common in KD (~ 10%)
  - Neurologic & GI findings are less common in KD

- KD is more common in patients of Asian descent, whereas MIS-C is more common in patients of African & Hispanic descent
- **Toxic shock syndrome**
  - Toxin-mediated systemic disease with shock & multiorgan failure caused by *Staphylococcus aureus* & *Streptococcus pyogenes*
- **Hemophagocytic lymphohistiocytosis (HLH)**
  - Gene-mediated or infection-/malignancy-triggered systemic hyperinflammation
  - Hemophagocytosis in liver, marrow, spleen, lymph nodes
- **Severe COVID-19 with hyperinflammation**
  - Respiratory symptoms are more prominent
  - MIS-C typically occurs 3-6 weeks after SARS-CoV2 exposure
- **Myocarditis of other etiologies**
  - Lack multisystem findings of MIS-C & temporal association with COVID-19
- **Infectious/inflammatory enterocolitis & appendicitis**
  - Lack multisystem findings of MIS-C & temporal association with COVID-19
- **ADEM**
  - Similar imaging but may not meet clinical definition
  - No temporal association with COVID-19
- **Postviral autoimmune encephalitis of other etiologies**
  - Similar encephalitis is also seen with herpes & West Nile virus infections
- **Other pediatric arteriopathies with acute stroke**
  - Moyamoya disease, arterial dissection, vasculitis

PATHOLOGY

General Features

- Single-stranded RNA virus
- Respiratory droplet transmission
- SARS-CoV2 binds ACE2 receptor & transmembrane serine protease 2 (TMPRSS2) & ↑ expression of proinflammatory cytokine IL-6, IL-8, & TNF-α
- ACE2 receptors are also found in heart, intestinal smooth muscle, liver, kidneys, neurons, & immune cells

CLINICAL ISSUES

Presentation

- Most common signs/symptoms
  - COVID-19
    - Fever, cough, sore throat, rhinorrhea, congestion, diarrhea, fatigue, dyspnea, rash, conjunctivitis
    - GI in > 50%: Diarrhea, abdominal pain, vomiting
    - ↑ CRP, ESR, LDH, D-dimer
    - Neutropenia, lymphopenia, thrombocytopenia
  - MIS-C CDC case definition
    - < 21 years old, fever, laboratory evidence of inflammation (↑ CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, or neutrophils, &/or ↓ lymphocytes or albumin), & evidence of clinically severe illness requiring hospitalization with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, GI, dermatologic or neurological), plus
    - No alternative plausible diagnoses, plus
    - (+) for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within 4 weeks prior to onset of symptoms
      - In largest study, 25.8% with (+) PCR test for SARS-CoV2 & 46.1% with (+) serology test for SARS-CoV2
- Other signs/symptoms
  - MIS-C
    - Neurologic in 31-47%: Headache, altered mental status, encephalopathy, seizure, coma, encephalitis, demyelinating disorder, aseptic meningitis
    - GI in 90.9%: Abdominal pain 61.9%, vomiting 61.8%, diarrhea 53.2%
    - Cardiovascular in 86.5%: Dysfunction 40.6%, shock 35.4%, myocarditis 22.8%, coronary artery aneurysm 18.6%
    - Dermatologic/mucocutaneous in 70.9%

Demographics

- Children account for ~ 6.5% of COVID-19 cases in USA
- COVID-19 & MIS-C are more common in patients of African & Hispanic descent
- Mean age of MIS-C patients: 8 years old

Natural History & Prognosis

- Children overall have milder disease with COVID-19
  - Account for ~ 1.5 % of hospitalizations & 0.3% of deaths related to COVID-19 in USA
  - 1/3 of hospitalized children need ICU, similar to adults
- In largest study of MIS-C patients describing 570 patients
  - 63.9% required ICU care, 62% required vasopressor support, 1.8% died

Treatment

- COVID-19
  - Remdesivir is available through Emergency Use Authorization or compassionate use in pediatric patients
  - Dexamethasone may benefit patients with respiratory disease who are on mechanical ventilation
- MIS-C
  - Immunomodulatory therapy: IVIG &/or glucocorticoids, anakinra (recombinant human IL-1 receptor antagonist) for refractory disease
  - Antiplatelet/anticoagulation therapy: Low-dose aspirin until normalization of platelet count & normal coronary arteries at ≥ 4 weeks after diagnosis; enoxaparin or warfarin if coronary artery z-score > 10.0; also consider anticoagulation if moderate-severe LV dysfunction

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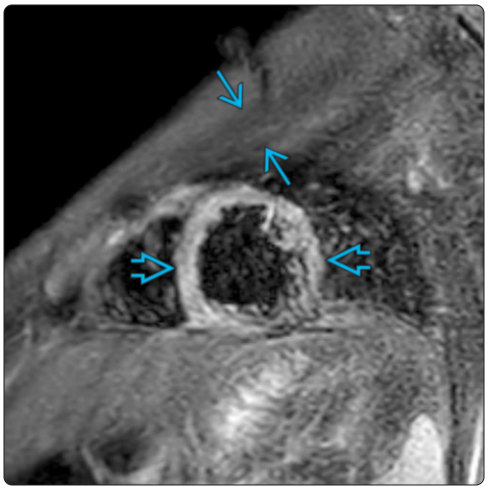
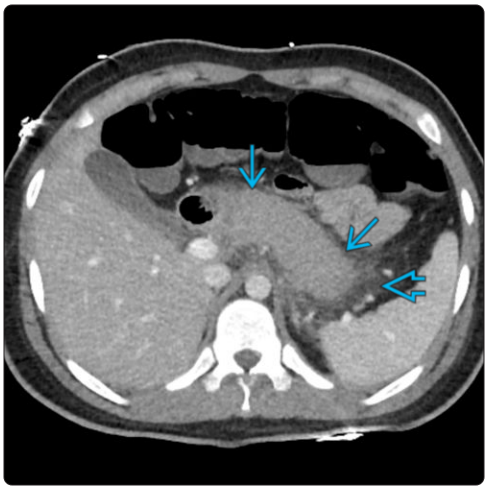
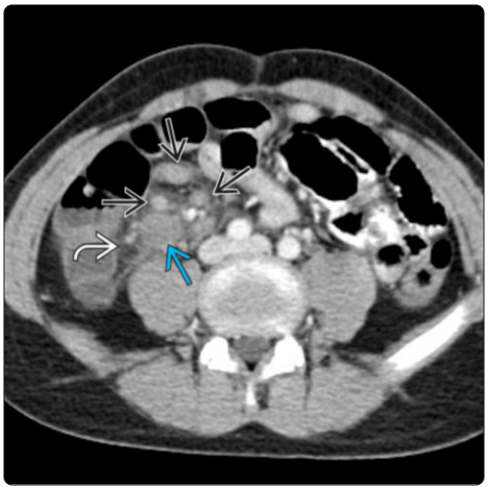
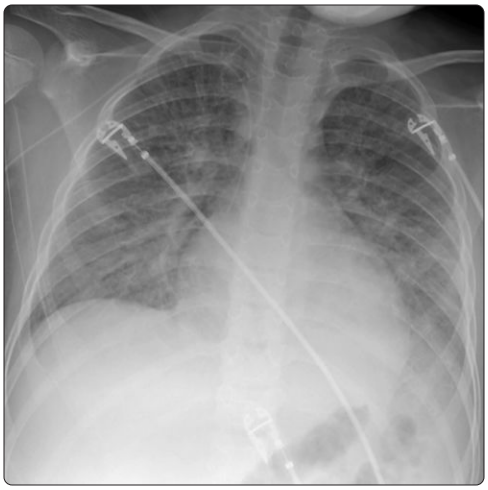


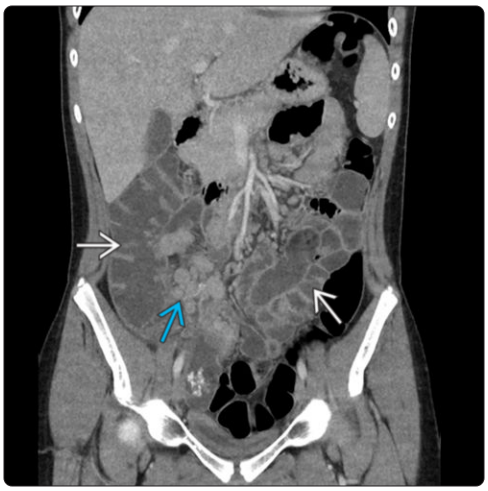


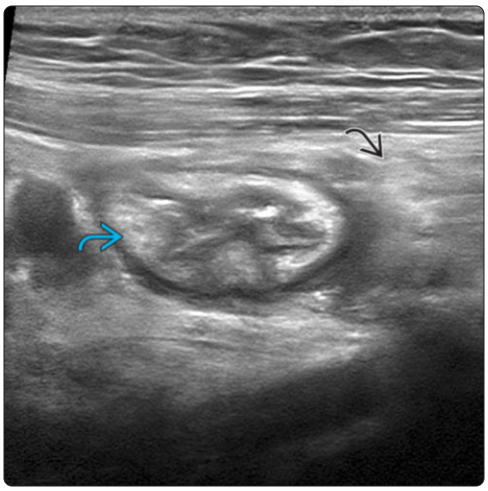
(Left) *Short-axis T2 STIR cardiac MR in a 16 year old with 10 days of fever & abdominal pain shows high signal intensity of the left ventricular (LV) myocardium vs. skeletal muscle (ratio of 2.5, with > 1.9 being abnormal), consistent with edema. COVID-19 IgG was positive, consistent with MIS-C.* **(Right)** *Axial CECT in the same patient shows diffuse pancreatic thickening & homogeneous enhancement with surrounding edema, consistent with acute interstitial edematous pancreatitis in MIS-C.*





(Left) *Axial CECT of a 15 year old with pain demonstrates inflammatory stranding at the right lower quadrant & multiple prominent lymph nodes, some with low density. The appendix was normal (not shown).* **(Right)** *Frontal radiograph in the same patient shows diffuse interstitial opacities compatible with pulmonary edema. Echocardiography showed LV dysfunction & ↓ LVEF. Inflammatory markers were elevated, & COVID-19 RT-PCR test was positive. The patient was diagnosed with MIS-C.*





(Left) *Coronal CECT in a 10 year old with right lower quadrant pain, fever, rash, & conjunctivitis shows multiple enlarged lymph nodes & fluid-filled bowel.* **(Right)** *Transverse US in the same patient shows distal ileal wall thickening & hyperechogenicity with adjacent fat induration. Serology was positive for COVID-19 exposure. Decreased systolic LV function & coronary artery ectasia were seen on echocardiography. The patient met the criteria for MIS-C & also had elevated inflammatory markers.*