Severe COVID-19 in children is rare. Case reports describe an emerging inflammatory syndrome with features of Kawasaki Disease and Toxic Shock Syndrome that may be related to COVID-19. This multisystem inflammatory syndrome in children (MIS-C) has also been termed pediatric multisystem inflammatory syndrome (PMIS) and pediatric inflammatory multisystem syndrome (PIMS). We summarize 5 articles describing MIS-C in hospitalized children in the US, UK, and France.

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A. **SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020,** Belot et al. Eurosurveillance (June 4, 2020).

**Key findings:**
- SARS-CoV-2-related MIS-C cases increased 4–5 weeks after peak COVID-19 hospitalizations (Figure).
- Compared with 48 children with MIS-C without SARS-CoV-2, 108 hospitalized children with SARS-CoV-2-related MIS-C were:
  - older (median 8 years vs. 3 years).
  - more likely to have heart inflammation (myocarditis) (70% vs. 10%).
  - more often critically ill (67% vs. 8%).

**Methods:** French nationwide surveillance for MIS-C cases, between March 1 to May 17, 2020. MIS-C defined as having at 1 or more symptoms of: inflammation of lining around the heart, lungs, or abdomen (serositis) or of heart muscle (myocarditis), symptoms of autoimmune macrophage activation syndrome, or Kawasaki-like disease. Evidence of SARS-CoV-2 defined by positive RT-PCR or serology test, direct link with a confirmed COVID-19 case, or suggestive radiography. **Limitations:** Use of non-standard case definition; definition of “SARS-CoV-2-related” did not require RT-PCR or IgG; unclear classification for 13 children.
Figure:

Note: Adapted from Belot et al. Weekly number of COVID-19 hospitalizations (right axis) and number of SARS-CoV-2-related MIS-C cases (left axis) in France, between March 1 to May 17, 2020. Licensed under CC-BY 4.0.


Key findings:
- Of 21 children and adolescents with MIS-C, median age 8 years, and 12/21 (57%) of African or Caribbean ancestry.
  - Median interval between SARS-CoV-2 contact and MIS-C was 36 days (range 18–45).
- All had GI symptoms, 16/21 (76%) had heart inflammation (myocarditis); half met criteria for Kawasaki disease; all had elevated IL-6.
- 17/21 (81%) were critically ill, including 8 with sustained hypotensive shock; none died.
- 8/21 (38%) had positive SARS-CoV-2 RT-PCR, 19/21 (90%) had SARS-CoV-2 IgG.

Methods: Clinical case-series of children and adolescents ≤18 years admitted to single hospital in France, between April 27 and May 11, 2020 with Kawasaki disease. Some might be included in Belot et al. Limitations: Single center; small sample; limited to those with Kawasaki-like disease.


Key findings:
- Among 58 children hospitalized with SARS-CoV-2-related MIS-C in England, all presented with fever, 31 (53%) with abdominal pain, 30 (52%) with diarrhea, and 30 (52%) with rash; 8 developed coronary artery aneurysms.
- 29/58 (50%) were critically ill: 27 were in shock, 25 required ventilation, 1 died.
- Children with SARS-CoV-2-related MIS-C were older (Figure 1) and had a trend towards greater inflammation (measured by C-reactive protein) than children with other non-SARS-CoV-2-related inflammatory disorders (Figure 2).
- SARS-CoV-2 IgG detected in 40/46 (87%) tested.
**Methods:** Clinical case-series from 8 hospitals in England, between March 23 and May 16, 2020. Cases met criteria for WHO, UK, or US case MIS-C definitions, but SARS-CoV-2 exposure not required for inclusion. **Limitations:** Cases identified through voluntary surveys, may not include all MIS-C cases.

Figure 1

![Figure 1 Diagram](image1)

**Note:** Adapted from Whittaker et al. Ages of hospitalized children with different inflammatory disorders. **Black horizontal lines** within boxes represent median ages (years), top and bottom of boxes represent 25th and 75th percentiles, with 95% confidence intervals (thin black line “whiskers”). Reproduced with permission from JAMA. doi:10.1001/jama.2020.10369. Copyright © 2020 American Medical Association. All rights reserved.

Figure 2

![Figure 2 Diagram](image2)

**Note:** Adapted from Whittaker et al. C-reactive protein (inflammation) levels of hospitalized children with different inflammatory disorders. **Black horizontal lines** within boxes represent median C-reactive protein levels, top and bottom of boxes represent the 25th and 75th percentiles, with 95% confidence intervals (thin black line “whiskers”). Reproduced with permission from JAMA. doi:10.1001/jama.2020.10369. Copyright © 2020 American Medical Association. All rights reserved.


**Key findings:**
- Of 44 hospitalized children in a New York hospital with MIS-C, median age was 7 years.
- GI symptoms (e.g., pain, nausea/vomiting, diarrhea, bleeding) were reported by 37/44 (84%).
  - 13 (30%) presented with fever and mild GI symptoms during the week prior to hospitalization.
- 11/44 (25%) required supplemental oxygen; 1 child was intubated; none died.
Methods: Clinical case-series of 44 hospitalized children and adolescents with MIS-C and exposure or evidence of current or recent SARS-CoV-2 infection, New York City, between April 18 and May 22, 2020. Limitations: MIS-C not defined; single center, may not be representative.

E. **Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City.** Cheung et al. JAMA (June 8, 2020).

**Key findings:**
- Of 17 hospitalized children and adolescents with SARS-CoV-2-related MIS-C, median age was 8 years (range 1.8–16); 12/17 (71%) were white; 3/17 (18%) had mild asthma.
- GI symptoms were reported by 14/17 (82%); 1 had acute bowel inflammation (ileocolitis).
- Moderate–severe cardiac dysfunction in 6/17 (35%); 1 had a coronary aneurysm.
- 15/17 (88%) were critically ill: 13 were in shock on presentation; none were intubated or died.
- IL-6 was elevated in 16/17 (94%).


Implications for 5 studies (Belot et al., Toubiana et al., Whittaker et al., Miller et al. & Cheung et al.): MIS-C can cause severe illness and seems to be a SARS-CoV-2 postinfectious complication. Patients with SARS-CoV-2-related MIS-C were older and required more intensive care than patients with Kawasaki disease. Pneumonia was noticeably absent; mechanical ventilation seemed to be used to support patients with cardiovascular collapse (shock) rather than respiratory failure. Early MIS-C with GI symptoms may be misdiagnosed as mild GI illness. Studies are needed to understand the spectrum of MIS-C severity, timing between SARS-CoV-2 infection and MIS-C, risk factors, possible long-term complications, and therapy.

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**Psychological distress and loneliness reported by US adults in 2018 and April 2020.** McGinty et al. JAMA (June 3, 2020).

**Key findings:**
- Prevalence of serious psychological distress among US adults was higher in April 2020 (13.6%) than in 2018 (3.9%) (Figure).
  - Distress was substantially higher in 2018 among adults ages 18–29 years, Hispanic/Latinos, and those in low income households (Figure).

Methods: Prevalence of self-reported psychological distress among ~27,000 adults (1,468: April 2020; 25,417: 2018) from 2 surveys with same questions. Weighted for nationally representative estimates. Limitations: Two surveys might have sampled different populations; possible overestimates if those with distress were more likely to respond.

Implications: A large proportion of US adults reported serious psychological distress in April 2020. Increased access to mental health and social support services, particularly for young adults, may be important.
Figure:

Note: From McGinty et al. Psychological distress among US adults aged ≥18 years overall and by group, April 2020 vs. 2018. April 2020 results (dark bars) are from the Johns Hopkins COVID-19 Civic Life and Public Health Survey. 2018 results (light bars) are from the National Health Interview Survey. Error bars show 95% CIs. Reproduced with permission from JAMA. doi:10.1001/jama.2020.9740. Copyright©2020 American Medical Association. All rights reserved.
Some patients with COVID-19 develop acute respiratory distress syndrome (ARDS), or extensive lung inflammation, in the second week of infection, characterized by low oxygen levels and severe shortness of breath. ARDS has 3 stages: exudative (fluid build-up, diffuse alveolar damage, and cellular debris lining the air sacs), proliferative (recovery and early scarring), and fibrotic (extensive scarring). Severe COVID-19 also causes abnormal clotting. These papers describe autopsy findings from adults who died from COVID-19.

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**Key findings:**
- Lungs from 38 Italian patients had extensive damage.
  - All showed exudative and proliferative phases of ARDS; none had fibrotic scarring (Figure A).
  - 33 (87%) also had diffuse small blood clots; none had bleeding.
- All lung samples had dead cells lining the air sacs (alveoli).
  - 9/10 samples had viral-like particles in or around cells lining alveoli, suggesting viral infection of these cells (Figure B).

**Methods:** Postmortem examination of lung tissue from 38 patients who died from COVID-19 in 2 hospitals in northern Italy, between February 29 and March 24, 2020. Patients had pre-existing comorbidities including hypertension (in 18), cardiovascular disorders (11), diabetes (9), and mild chronic obstructive pulmonary disease (3). **Limitations:** Patient hearts were not examined; illness duration was not provided.

**Figure:**

Note: Adapted from Carsana *et al*. A. Early phase alveolar damage showing thick cellular debris (hyaline membrane; red arrowhead) lining an alveolus (circled in blue). B. Electron microscope image of virion-like particles inside (red arrow) and along the surface (red arrowheads) of lung cells. This article was published in Lancet Infectious Diseases, Vol 20, Carsana *et al*., Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study, Page Nos, Copyright Elsevier 2020. This article is currently available at the Elsevier COVID-19 resource center: https://www.elsevier.com/connect/coronavirus-information-center.

Key findings:
- Autopsies of 10 African American patients showed extensive lung damage.
  - All lungs showed diffuse alveolar damage; the extent varied and was fibrotic in one patient.
  - Lungs also showed blood clots, injured blood vessels, and, in 9 patients, bleeding (Figure A&B).
- Several hearts were enlarged, probably from difficulty pumping blood through damaged lungs (Figure C).
  - Heart inflammation (myocarditis) was not observed.

Methods: Autopsies of 10 African American patients (44–78 years) who died from COVID-19, New Orleans, LA. All patients had hypertension, diabetes, or obesity. Limitations: Lacked control groups without COVID-19 or without comorbidities.

Figure:

Note: Adapted from Fox et al. A. Swollen lungs with dark patches of bleeding. B. Green arrows show blood clots within small vessels. C. Cross-section of a heart with significantly dilated right ventricle (RV). Approximate normal RV size shown with red outline. This article was published in Lancet Respiratory Medicine, Vol 8, Fox et al., Pulmonary and cardiac pathology in African American patients with COVID-19: An autopsy series from New Orleans, Page 681-686, Copyright Elsevier 2020. This article is currently available at the Elsevier COVID-19 resource center: https://www.elsevier.com/connect/coronavirus-information-center.


Key findings:
- Lungs from 10 German patients showed diffuse alveolar damage (Figure).
  - Destructive fibrotic scarring in one immunocompromised patient.
  - Bleeding and clots were not observed.
- Mild inflammation of the heart and heart lining were seen in 4 and 2 patients, respectively, but did not meet criteria for true myocarditis.
**Methods:** Autopsies of 10 patients with COVID-19 (64–90 years), April 4–19, 2020, Germany. Patients had pre-existing comorbidities including hypertension (6), coronary disease (5), obesity (2), an enlarged heart (2), and emphysema (2). **Limitations:** Small sample size; race/ethnicity were not reported.

**Figure:**


**Implications for 3 studies (Carsana et al., Fox et al. & Schaller et al.):** As with SARS, diffuse alveolar damage was the cause of death in these COVID-19 patients. Unlike SARS, blood clots in lung blood vessels contributed to some deaths, and is consistent with prior reported observations of excess pulmonary embolism covered in Science Update 2020-05-12. Better understanding of abnormal clotting and bleeding in COVID-19 and factors that influence outcomes may inform clinical practice and the search for new treatments.

**In Brief**

**Non-Pharmaceutical Interventions**

- Wise J. COVID-19: Sweden should have done more, says architect of country’s strategy. BMJ. The epidemiologist responsible for Sweden’s light-touch response admits Sweden should have done more.
- Hall et al. The legal authority for states’ stay-at-home orders. NEJM. Discusses legal challenges to public health orders imposed during the coronavirus pandemic.
- Haushofer et al. Which interventions work best in a pandemic? Science. Non-pharmaceutical interventions (NPIs) are often implemented without evidence that they work. Authors describe practical ways to use RCTs to evaluate NPIs in a pandemic setting.

**Health Equity**

Success Stories

- Avitzur O. In Greece, COVID-19 numbers are very low. Neurologists explain why. Neurology Today. Neurologists practicing in Greece describe actions taken to stave off the spread of coronavirus and speculate why they worked.

Other Topics

- Ledford H. The coronavirus outbreak could make it quicker and easier to trial drugs. Nature. Remote clinical trials and streamlined processes are a few ways that the coronavirus pandemic may permanently transform how clinical trials are conducted.

Journal Retractions

- Several high-profile retractions have brought attention to challenges posed by rapidly publishing scientific data during the coronavirus pandemic.
  - King et al. Fast news or fake news? The advantages and the pitfalls of rapid publication through pre-print servers during a pandemic. EMBO reports.