

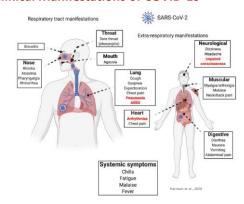
Outline

- Pulmonary
- Multisystem Inflammatory Syndrome in children associated with COVID-19 (MIS-C)
- Cardiovascular
- Neurological
- Other
- Post COVID-19 vs long COVID





Clinical Manifestations of COVID-19



Conditions associated with increased risk of severe COVID-19 in children

- Diabetes
- Hypertension
- · Cardiac disease
- · Chronic lung disease
- Cerebrovascular disease
- Chronic kidney disease
- Immunosuppression
- Cancer
- Obesity
- Asthma

WHO. 2020: CDC. 2022





Severity of illness in children with COVID-19 Critical 1.2% Asymptomatic 14.2% Moderate 46.0% Mild 36.3% Souza et al., 2020 Souza et al., 2020

Pulmonary Manifestations & Complications

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Pulmonary Manifestations & Complications Clinical stages of COVID-19 Pulmonary disease: Early stage: edema, epithelial damage, and inflammation of capillaries and endothelium (day 0-1) • Exudative diffuse alveolar damage stage (days 1-7) • Organizing pneumonia stage (1 week to several weeks) · The fibrotic stage (weeks to months) UB|MD PEDIATRICS **Chest CT Features Associated With Mild to Moderate COVID-19 Pneumonia** Kunhua et al., 2020 UB|MD PEDIATRICS **Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia**

Kunhua et al., 2020

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Recommendations on the initial management of hypoxic COVID-19 patients

Therapy	Implementation
High-flow nasal oxygen	Might prevent or delay the need for intubation
Tidal volume	Use 6 mL/kg per predicted bodyweight (can reduce to 4 mL/kg per predicted bodyweight)
Plateau airway pressure	Maintain at <30 cm H ₂ 0 if possible
Positive end-expiratory pressure	Consider moderate to high levels if needed
Recruitment manoeuvres	Little value
Neuromuscular blockade	For ventilator dyssynchrony, increased airway pressure, hypoxaemia
Prone positioning	For worsening hypoxaemia, PaO ₂ FIO ₂ <100-150 mm Hg
Inhaled NO	Use 5–20 ppm
Fluid management	Aim for negative fluid balance of 0.5–1.0 L per day
Renal replacement therapy	For oliguric renal failure, acid-base management, negative fluid balance
Antibiotics	For secondary bacterial infections
Glucocorticoids	Not recommended
Extracorporeal membrane oxygenation	Use EOLIA trial criteria ³

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Supplemental oxygen delivery





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Supplemental oxygen delivery





Mechanical Ventilation

Extra-corporeal Membrane Oxygenation (ECMO)

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Thoranios for COVID 19	
Therapies for COVID-13	
Hospitalization Onset of Savara	
Unset of Severe Exposure symptoms symptoms Survival	
Vaccines	
Monoclonal antibodies Death	
Antivirals	
Dexamethasone	
Immunomodulators	
(2011) 1040 XII	
Jacobs School of Medicine July July	
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Anti-SARS-CoV-2 monoclonal antibodies with	
Emergency Use Authorizations from FDA:	
Tixagevimab co-packaged with cilgavimab	
Indicated for pre-exposure prophylaxis • Sotrovimab	
Indicated for post-exposure prophylaxis.	
Bebtelovimab	
Indicated for post-exposure prophylaxis.	
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Antiviral Drugs in development	
Antivital brugs in development	
Remdesivir	
Nucleoside analogue	
 Intravenous remdesivir is approved by the FDA for the treatment of COVID-19 in adult and pediatric patients (aged ≥12 	
years and weighing ≥40 kg).	
 It is approved for the treatment of mild to moderate COVID-19 in high-risk, nonhospitalized patients (i.e., a 3-day course 	
initiated within 7 days of symptom onset) and for the treatment	
of hospitalized patients with COVID-19 (i.e., a 5-day course)	
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University a Buddle	

Antiviral Drugs in development

Nirmatrelvir-ritonavir

It's a protease inhibitor combination

• FDA EUA for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 yo and older weighing at least 40 kg) with positive results of SARS-CoV-2 and who are at high risk for progression to severe COVID-19, including hospitalization or death





Antiviral Drugs in development

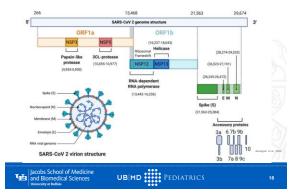
Molnupiravir

- · It's a pyrimidine ribonucleoside analog that inhibits RdRp of SARS-CoV-2 to induce RNA mutagenesis
- FDA EUA for the treatment of mild-to-moderate COVID19 in adults with positive results of direct SARS-CoV-2 who are at high risk for progression to severe COVID-19, including hospitalization or death
- No authorized for patient <18 year of age





Genomic Organization of SARS-CoV-2



Multisystem inflammatory syndrome in children (MIS-C)





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Multisystem inflammatory syndrome in children (MIS-C)

Case definition for MIS-C:

•An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND

- •No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.





Common signs and symptoms of MIS-C

- Kawasaki disease-like features
- Gastrointestinal: abdominal pain, diarrhea, nausea/vomiting
- Toxic shock syndrome-like features with hemodynamic instability and poor heart function
- Cytokine storm/macrophage activation or hyperinflammatory features.
- · Thrombosis or acute kidney injury
- Shortness of breath suggestive of congestive heart failure or pulmonary embolism

CDC, 2022

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Recommended testing for MIS-C

- COVID-19 testing:
 - RT-PCR assay
 - Serologic testing
- Expanded laboratory tests including pro-BNP, triglycerides, creatine kinase, amylase, blood and urine culture, D-dimer, prothrombin time/partial thromboplastin time (PT/PTT), INR, CRP, ferritin, LDH, comprehensive metabolic panel, and fibrinogen
- Chest radiograph, EKG, Echo and troponin. If abnormal, consult pediatric cardiology and consider additional diagnostic testing for myocardial injury

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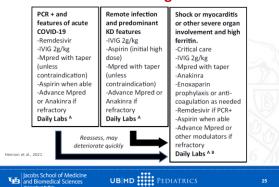
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Common laboratory findings in MIS-C

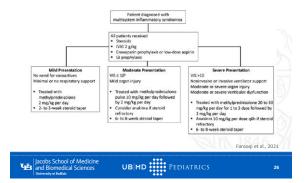
- An abnormal level of inflammatory markers in the blood, including
 - Elevated ESR/CRP
 - Eleveted ferritin
 - Elevated LDH
- Lymphopenia <1000,
- Thrombocytopenia <150,000, neutrophilia.
- Elevated B-type natriuretic peptide (BNP) or NTproBNP (pro-BNP),
- Hyponatremia
- Elevated D-dimers

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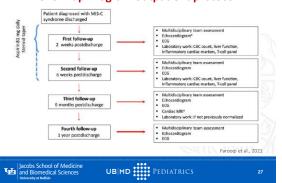
MIS-C treatment guideline



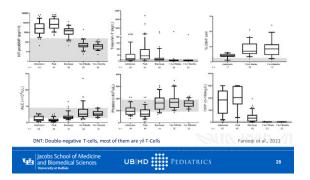
MIS-C inpatient management



Columbia University Interdisciplinary MIS-C Follow-up Program outpatient protocol



Laboratory trend in patients with MIS-C over the follow-up period



Cardiac manifestations and complications





Cardiac manifestations and complications

- · Myocardial injury:
 - Definition: Elevated cardiac troponin levels suggest myocardial injury. Conditions associated with myocardial injury include:
 - Myocarditis (Rajpal, 2020, Daniels, 2021)
 - Myocardial infarction: STEMI patients with concurrent COVID-19 infection have worse outcomes (Choudry, 2020)
 - Stress cardiomyopathy (Fried, 2020)
 - Cardiogenic shock: Myocarditis or infarction can be further complicated by cardiogenic shock (Fried, 2020)
 - Arrhythmias: Patients with myocardial injury, infarction, shock, and or electrolyte disturbances are prone to arrythmias (Wang, 2020)
- Heart failure: Heart failure may be precipitated by acute on chronic heart disease, acute hemodynamic stress or from myocardial injury in patients with COVID-19 (Chen. 2020, Zhou, 2020)





Myocarditis and Pericarditis after mRNA COVID-19 Vaccines Among Adolescents and Young Adults

- Cases of myocarditis and pericarditis have been reported in the United States after mRNA COVID-19 vaccination (mRNA SARS-CoV2 SP). This was not observed after receipt of the adenovirus-based COVID-19 Vaccine
- Reported cases have occurred predominantly in male adolescents and young adults 16 years of age and older
- Onset was typically within several days after mRNA COVID-19 vaccination
- Cases have occurred more often after the second dose than the first dose





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Myocarditis and Pericarditis after mRNA COVID-19 Vaccines Among Adolescents and Young Adults

- Clinical manifestations: acute chest pain, shortness of breath, or palpitations. In this younger population, coronary events are less likely to be a source of these symptoms.
- Evaluation: ECG, troponin level, and inflammatory markers (C-reactive protein, procalcitonin, erythrocyte sedimentation rate).
- For suspected cases, consider consultation with cardiology for assistance with cardiac evaluation and management. Evaluation and management may vary depending on the patient age, clinical presentation, potential causes





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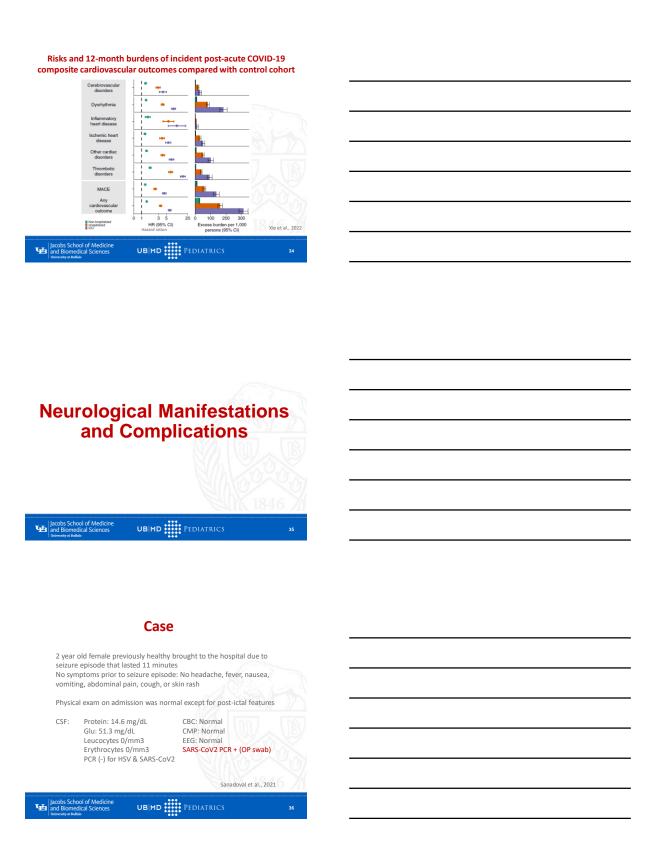
Long-Term Cardiovascular Outcomes of COVID-19

- In a cohort of patients who survived the first 30 days after COVID-19 diagnosis, risk of incident cardiovascular disease was increased over the ensuing 12 months
- Population burdens of heart failure and atrial fibrillation were particularly increased among COVID-19 patients
- For all cardiovascular diagnoses, risk increased with greater severity of the acute infection

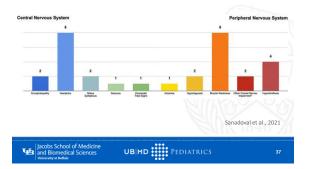
Xie et al., 2022

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Clinical features in children with new-onset neurologic manifestations associated with SARS-CoV-2 infection



Neurologic complications in hospitalized patients with COVID-19

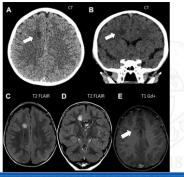
- Headache
- Impaired consciousness
- Stroke
- Seizure
- Meningitis
- Encephalitis
- Necrotizing encephalopathy
- Guillain-Barré syndrome
- Acute demyelinating encephalomyelitis

Koralnik, 2020; Mao, 2020)





Case 2. Head CT and Brain MRI



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SARS-CoV-2 is associated with changes in brain structure

- Greater reduction in grey matter thickness and tissuecontrast in the orbitofrontal cortex and parahippocampal gyrus,
- Greater changes in markers of tissue damage in regions functionally-connected to the primary olfactory cortex
- · Greater reduction in global brain size.

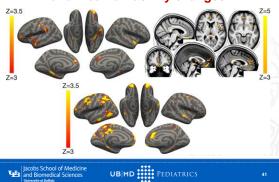
Douaud et al., 2022



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Differences in grey matter thickness and mean diffusivity changes



Reduction in grey matter thickness and intensity contrast

Temporal piriform cortex functional network (OD)

Controls

Cases

6

Controls

Cases

6

Cases

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Cases

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Cases

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Post-COVID-19 conditions vs Long COVID-19





Post-COVID-19 conditions vs Long COVID-19

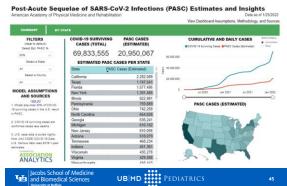
- · The CDC recommends using the umbrella term "post-COVID conditions" for a wide range of signs and symptoms that occur 4 or more weeks after acute COVID-19 infection
- · Post-COVID conditions are characterized by a lack of return to a usual state of health following COVID-19
- · The mechanism of post-COVID conditions is not well understood. I may be secondary to virus-specific pathophysiologic changes, prolonged inflammatory response to the acute infection and sequelae of postintensive care illness

Hosey, 2020; Inoue, 2019)

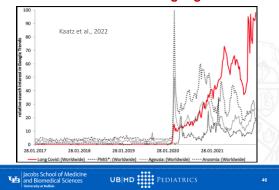




Post-COVID-19 conditions, in numbers



Post-COVID-19 conditions google searches



Post-COVID-19 conditions vs Long COVID-19

- · Common symptoms include:
 - · Fatigue,
 - · Shortness of breath,
 - · Cognitive dysfunction
- · Symptoms may be:
 - New onset, following initial recovery from an acute COVID-19 episode
 - Persist from the initial illness
 - · Symptoms may also fluctuate or relapse over time





Post-COVID-19 conditions

- Almost 10% of children aged 2-11 years and 13% aged 12-16 years reported one or more lingering symptoms 5 weeks after COVID-19 infection
- Another study found that 25% of hospitalized children surveyed after discharge reported symptoms more than 5 months later
- A national survey in the Netherlands showed that among 89 children suspected of having long COVID, 18% were admitted to the hospital due to their longterm symptoms

Brackel, 2021; Osmanov, 2022





Conclusions

- COVID-19 is associated with complications in children
- The proportion of complications and sequelae of COVID-19 in children is lower than in adults
- The most common complications of COVID-19 in children are pulmonary, cardiac, neurological and gastrointestinal
- Multisystemic inflammatory syndrome in children associated with COVID-19 is the most common complication not related to SARC-CoV2 replication
- Long COVID-19 affects children and information on screening, diagnosis, treatment, and prognosis are to be defined



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Thank You!

Questions?





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