

COVID-19 COMPLICATIONS AND LONG TERM EFFECTS OF COVID-19 IN CHILDREN

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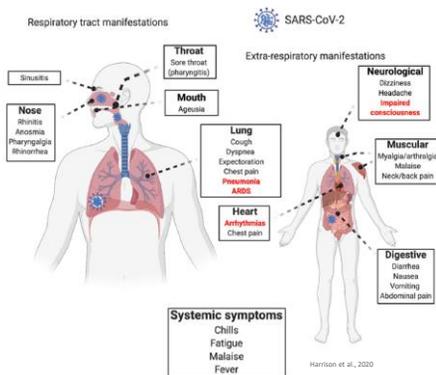
Outline

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



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Clinical Manifestations of COVID-19



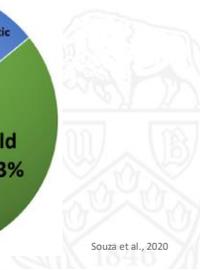
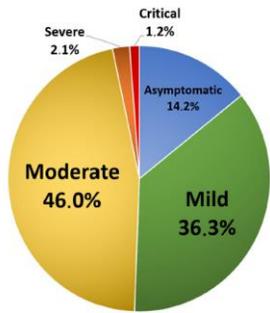
Conditions associated with increased risk of severe COVID-19 in children

- 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



Souza et al., 2020

Pulmonary Manifestations & Complications



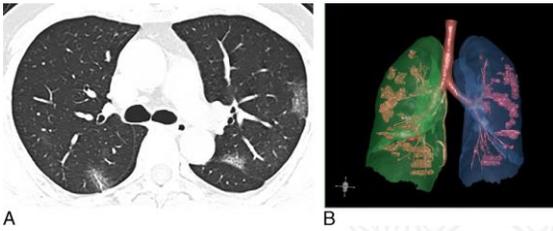
Pulmonary Manifestations & Complications

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)

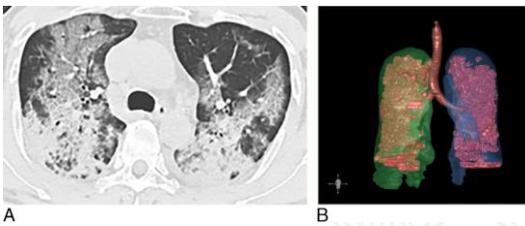
Bösmüller, February 2021

Chest CT Features Associated With Mild to Moderate COVID-19 Pneumonia



Kunhua et al., 2020

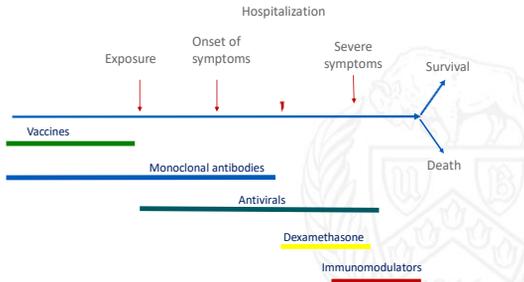
Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia



Kunhua et al., 2020

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Therapies for COVID-19



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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

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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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

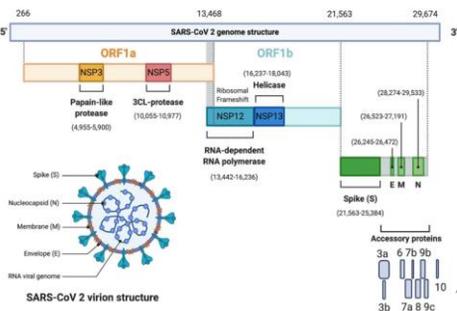
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Antiviral Drugs in development

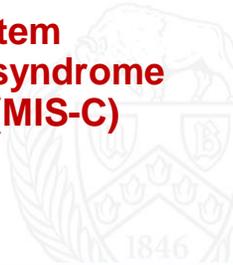
Molnupiravir

- 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)



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.

CDC, 2022

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



Blatz et al., 2021; Pessoa et al., 2021

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

CDC, 2022

Common laboratory findings in MIS-C

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

CDC, 2022

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

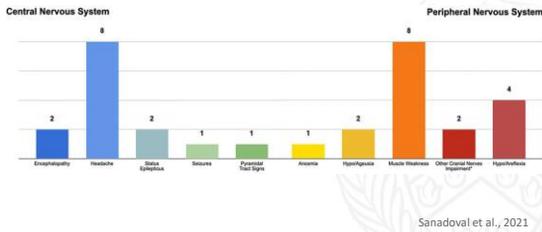
Myocarditis and Pericarditis after mRNA COVID-19 Vaccines Among Adolescents and Young Adults

- 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

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

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

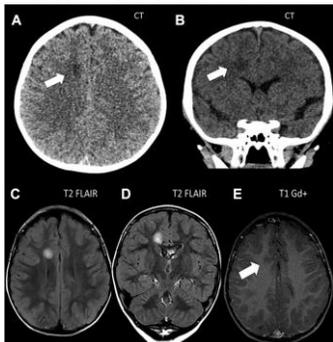


Neurologic complications in hospitalized patients with COVID-19

- 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



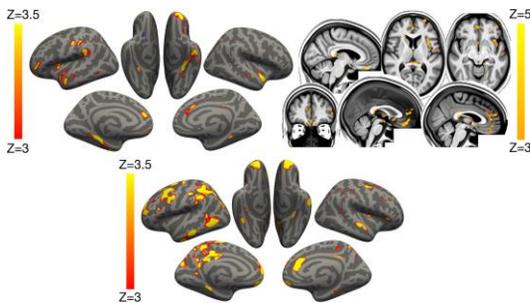
SARS-CoV-2 is associated with changes in brain structure

- Greater reduction in grey matter thickness and tissue-contrast 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

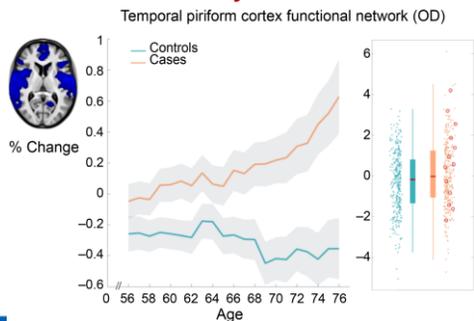
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Differences in grey matter thickness and mean diffusivity changes



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Reduction in grey matter thickness and intensity contrast



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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 SARS-CoV2 replication
- Long COVID-19 affects children and information on screening, diagnosis, treatment, and prognosis are to be defined

Thank You!

Questions?
