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

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

Severity of illness in children with COVID-19

- Severe: 2.1%
- Critical: 1.2%
- Asymptomatic: 14.2%
- Moderate: 46.0%
- Mild: 36.3%

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)

Koelmüller, 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
Recommendations on the initial management of hypoxic COVID-19 patients

Supplemental oxygen delivery

Supplemental oxygen delivery

Electronic supplementary information

Mechanical Ventilation

Extra-corporeal Membrane Oxygenation (ECMO)
Therapies for COVID-19

Hospitalization
- Exposure
- Onset of symptoms
- Severe symptoms
- Survival

Vaccines
Monoclonal antibodies
Antivirals
Dexamethasone
Immuno-modulators

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.

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)
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

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)

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
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

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),
  - Hypoatremia
  - Elevated D-dimers
MIS-C treatment guideline

- If patient is intubated or needs ventilator support
- Thrombolysis or heparin
- Aspirin or anticoagulation

Remote infection and predominant KD features
- IVG 2g/kg
- Aspirin (initial high dose)
- Advanced Mpro or Anakinra if refractory
- Daily Labs +

Shock or myocarditis or other severe organ involvement and high ferritin
- Critical care
- IVG 2g/kg
- Advanced Mpro or Anakinra
- Enoxaparin prophylaxis or anti-coagulation as needed
- Remdesivir if PCR+
- Aspirin when able
- Advanced Mpro or other modifiers if refractory
- Daily Labs +

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

• **Myocardial injury:**
  - Definition: Elevated cardiac troponin levels suggest myocardial injury. Conditions associated with myocardial injury include:
    - Myocarditis (Rajpal, 2020; Danesh, 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 (Rowe, 2020)
    - Arrhythmias: Patients with myocardial injury, infarction, shock, and or electrolyte disturbances are prone to arrhythmias (Rowe, 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

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
Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes compared with control cohort

Neurological Manifestations and Complications

Case

2 year old female previously healthy brought to the hospital due to seizure episode that lasted 11 minutes. No symptoms prior to seizure episode: No headache, fever, nausea, vomiting, abdominal pain, cough, or skin rash.

Physical exam on admission was normal except for post-ictal features.

CSF:
- Protein: 14.6 mg/dL
- Glu: 51.3 mg/dL
- Leucocytes 0/mm3
- Erythrocytes 0/mm3
- PCR (−) for HSV & SARS-CoV2

SARS-CoV2 PCR (+) (OP swab)

Sanadovol et al., 2021
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

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

Differences in grey matter thickness and mean diffusivity changes

Reduction in grey matter thickness and intensity contrast
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. It may be secondary to virus-specific pathophysiologic changes, prolonged inflammatory response to the acute infection and sequelae of post-intensive care illness.

Post-COVID-19 conditions, in numbers

- COVID-19 surviving cases (total): 69,833,555
- COVID-19 surviving cases (estimated): 20,950,067
- Estimation PSC cases per State (CDC Case Estimates)
- COVID-19 surviving cases (estimated)

Hosey, 2020; Inoue, 2019
### Post-COVID-19 conditions google searches

![Graph showing Post-COVID-19 conditions search trends]

Kautz et al., 2022

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### 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

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### 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 long-term 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

Thank You!
Questions?