Multisystem Inflammatory Syndrome in Children (MIS-C)

Advisory Committee to the Director, NIH

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Multisystem Inflammatory Syndrome in Children (MIS-C)

- MIS-C is characterized by fever, along with multiorgan inflammation, often with cardiovascular dysfunction.
- Severe GI pain is more common in MIS-C than in related conditions.
- Children become critically ill quickly, but most recover, generally within one week.

MIS-C Organ System Involvement and Disease Patterns

- Respiratory: 50.3%
- Cardiovascular: 79.3%
- Gastrointestinal: 85.6%

Outcome
- ICU admission: 73.3%
- Mortality: 1.9%

SARS-CoV-2
- RT-PCR positive: 37.5%
- IgG positive: 63.6%
- Close contacts: 28.1%

Mild disease course: 14%
Severe disease course: 86%

n=953

Hoste et al. (2021)
• COVID-19 hospitalization rate increased for children and adolescents after Delta variant emerged.

• Statistics are updated monthly; MIS-C numbers have not decreased.

5,526 confirmed cases
48 total deaths

https://www.cdc.gov/mis/cases/index.html

Data as of: 11/1/21
Major Challenges in MIS-C

• How to define/diagnose MIS-C and distinguish it from similar conditions such as Kawasaki disease and severe COVID-19?

• How to predict who is at risk for MIS-C?
  • Approximately 1 in 1000-3000 children who have SARS-CoV-2 will develop MIS-C three to four weeks after the initial infection

• How to treat MIS-C?

• How should children with MIS-C be followed long-term?
How to define/diagnose MIS-C?
Predicting Viral-Associated Inflammatory disease severity in children with Laboratory diagnostics and artificial Intelligence (PreVAIL kIds)

• Develop translational tools to understand the spectrum of pediatric SARS-CoV-2 illness, rapidly diagnose and characterize MIS-C associated with SARS-CoV-2, and predict the longitudinal risk of disease severity after exposure to and/or infection by SARS-CoV-2
  o Genetics; omics; other biomarkers
  o Viral dynamics and immune profiling studies
  o Digital health platforms leveraged for children
  o Artificial intelligence

• Milestone-driven award (R61/R33); up to 4 years

• https://www.nichd.nih.gov/newsroom/news/122120-prevail-kids

* Note: MIS-C is one of most well-characterized forms of post-acute sequelae of SARS-CoV-2 (PASC) in children
PreVAIL kids Investigators and Approaches

- Severity predictors integrating salivary transcriptomics and proteomics with neural network intelligence in SARS-CoV-2 infection in children
  - Usha Sethuraman

- COVID-19 Network of networks expanding clinical and translational approaches to predict severe illness in children
  - Lawrence Kleinman

- Data science approach to MIS-C identification and management associated with SARS-CoV-2 infection and Kawasaki Disease in children
  - Cedric Manlhiot

- Diagnosis of MIS-C in febrile children
  - Audrey R. Odom John

- Artificial Intelligence COVID-19 Risk Assessment for kids
  - Ananth V. Annapragada

- Identifying biomarker signatures of prognostic value for MIS-C
  - Juan Salazar

- Discovery and clinical validation of host biomarkers of disease severity and MIS-C in children with COVID-19
  - Charles Chiu

PreVAIL Kids Data Coordinating Center

UC San Diego
Lucila Ohno-Machado

UC San Diego

Johns Hopkins University

C. Michigan University

RW Johnson Medical School

Baylor Coll. of Medicine

Children's Hosp. of Philadelphia

Conn. Children's Medical Center

UC San Francisco

https://www.radxrad.org/awardees/prevail-kids/
PreVAIL kids Prospective Enrollments – Ahead of Target

Prospective Enrollment Summary

Prospective Enrollment Breakdown (Actuals)

Legend
- Actual Accruals trendline
- Target Accruals trendline

Enrolled Participants

0 500 1,000 1,500 2,000 2,500 3,000 3,500 4,000 4,500 5,000


4,587 enrolled as of October, 2021

3,653 Participant Target

Control Febrile Controls Kawasaki Disease Severe Non-Severe MIS-C Total Enrollment

78 1,570 430 1,472 324 713 4587
Overview of PreVAIL kids-associated Publications and Presentations

BY THE NUMBERS

30
Published articles from the cohort

6
Presentations by PIs

Sample presentation venues include:

  Epub 2021 Feb 25.

Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data


Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19


Clinical performance of a semi-quantitative assay for SARS-CoV-2 IgG and SARS-CoV-2 IgM antibodies


Tackling Ordinal Regression Problem for Heterogeneous Data: Sparse and Deep Multi-Task


Characterization of SARS-CoV-2 and common cold coronavirus-specific T-cell responses in MIS-C and Kawasaki disease children

- Li-En Hsieh, Alba Grifoni, John Sidney, Chihiro Shimizu, Hinko Shike, Nanda Ramchandar, Elizabeth Moreno, Adriana H Tremoulet, Jane C Burns, Alessandra Franco.
How to predict who is at risk for MIS-C?
PreVAIL Kids Progress To Date

• In addition to the prospective cohort, five of the groups have enrolled 21,651 patients retrospectively across all clinical phenotypes, from mild to severe COVID-19 and MIS-C

• Early results have identified:
  • Potential signatures of 4 genes that distinguish MIS-C from Kawasaki disease, bacterial and other viral infections
  • Specific cytokines in saliva that may predict disease severity
  • Four projects have initiated discussions with company partners for commercialization support
NIH Intramural MIS-C Research (NIAID)

- Longitudinal, multi-institutional study used multi-omics to identify novel time- and treatment-related immunopathological signatures in children with COVID-19 and MIS-C
  - Differentiated immune responses for pediatric COVID-19 compared to MIS-C
  - Association of MIS-C with certain HLA alleles suggests genetic susceptibility

Sacco K et al. September 27, 2021
How to treat MIS-C?
• Pharmacokinetics of drugs used to treat COVID-19 in children, expanded to study MIS-C

• Observational study, MIS-C and pediatric COVID, currently at 33 sites
  • Approximately 420 SARS-CoV-2 positive
  • ~100 with MIS-C

• 102 treated with remdesivir; approved for treatment down to age 12
  • ~40 participants less than 12 years
  • Pharmacokinetic data pending; could lead to label change
Effects of intravenous immunoglobulin treatment for MIS-C

Works by reducing activated IL-1β+ neutrophils

Second line drugs include steroids, immunosuppressive drugs such as anakinra (anti IL-1) and infliximab (TNF blocker)
How should children with MIS-C be followed long-term?
CARING for Children with COVID
(Collaboration to Assess Risk and Identify Long-term outcomes for Children with COVID)

• Leverages networks from NICHD, NHLBI, NIAID to study MIS-C

  • Capitalizes on strengths of each network: immune profiling (NIAID); long-term cardiac effects (NHLBI); PK/PD of drugs used to treat COVID-19 but not labeled for children (NICHD)

  • Aim to follow children for five years through longitudinal protocol

  • Currently >1200 children enrolled across three protocols (>20% of MIS-C cases in the U.S)

  • Broad geographic reach; 20-30 sites for each protocol (limited overlap)
CARING for Children with COVID

- **Long-Term Outcomes after the Multisystem Inflammatory Syndrome in Children (MUSIC) (MIS-C patients)**
  - **Primary aim:** Characterize coronary artery abnormalities and left ventricular dysfunction
  - **Birepository:** Includes 477 samples; 49 complete trios; more than 1000 cardiac echos
  - Enrolling both retrospectively and prospectively; 4 sites in IDeA states
  - Design paper in American Heart Journal; 3-5 manuscripts planned for next few months

- **Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) (MIS-C and acute COVID-19 patients)**
  - 1-year observational study of clinical outcomes and immunophenotyping
  - Includes pre-treatment and immediate post-treatment biospecimens for analysis
  - First release of clinical results expected in Q1 2022
Data Interoperability is Vital to Maximize Understanding of COVID-19 Infection and MIS-C in Children

• A searchable data set for **interoperable sharing across different platforms**
  
  • Data platforms maximize data sharing & FAIRness (*Findability, Accessibility, Interoperability, and Reusability*)
  
  • First data released from the NICHD POPS study (~50 patients) in October 2021; larger batch of data under curation for release in the next couple months
  
  • Using HL7® FHIR® as an interoperability framework, facilitating data sharing with intent for iterative & continued collaboration
    
    • FHIR is the bridge from hospital-based data to research
  
  • NICHD has led development of pediatric Common Data Elements that can be used across COVID-19 research projects ([https://tools.niehs.nih.gov/dr2/index.cfm/resource/24250](https://tools.niehs.nih.gov/dr2/index.cfm/resource/24250))
Successful multi-PI PreVAIL klds Collaboration

CLOCK
(Collaborative Long-term study of Outcomes of COVID-19 in Kids)

RECOVER is Powered by Collaboration
Thank you!

Questions?