Multisystem Inflammatory Syndrome in Children (MIS-C)

Advisory Committee to the Director, NIH

Diana W. Bianchi, M.D.

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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

<table>
<thead>
<tr>
<th>System</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>99.4%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>50.3%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>79.3%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>85.6%</td>
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</tbody>
</table>

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

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

n=953

Hoste et al. (2021)
Daily MIS-C and COVID-19 CASES

- 5,526 confirmed cases
- 48 total deaths

- COVID-19 hospitalization rate increased for children and adolescents after Delta variant emerged
- Statistics are updated monthly; MIS-C numbers have not decreased

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

PreVAIL kIds

Data Coordinating Center

UC SAN DIEGO

JOHNS HOPKINS UNIVERSITY

C. MICHIGAN UNIVERSITY

RW JOHNSON MEDICAL SCHOOL

BAYLOR COL. OF MEDICINE

CHILDREN’S HOSP. OF PHILADELPHIA

CONN. CHILDREN’S MEDICAL CENTER

UC SAN FRANCISCO

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

Diagnosing and predicting risk in children with SARS-CoV-2 related illness
Jane Burns

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

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

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

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

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

Prospective Enrollment Summary

- 4,587 enrolled as of October, 2021
- 3,653 Participant Target

Prospective Enrollment Breakdown (Actuals)

- Control: 78
- Febrile Controls: 1,570
- Kawasaki Disease: 430
- Severe: 1,472
- Non-Severe: 324
- MIS-C: 713
- Total Enrollment: 4,587
Overview of PreVAIL klds-associated Publications and Presentations

BY THE NUMBERS

30
Published articles from the cohort

6
Presentations by PIs

Sample presentation venues include:

- AAP VIRTUAL 2021 National Conference & Exhibition
- The 13th International Kawasaki Disease Symposium

Sample articles:

- Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data
  - Tiphanie P Vogel, Pamela Maceri, Lisa, Nicola P Klein, EBA

- 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-CoV2 IgG and SARS-CoV2 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, Chisato Shimizu, Hiroko Shuke, 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
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
  - **Biorepository:** 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
Successful multi-PI PreVAIL kids Collaboration

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

MPIs: Kleinman, Annapragada, Chiu, Manlhiot, Salazar & Sethuraman

RECOVER is Powered by Collaboration
Thank you!

Questions?