Agenda Part 1- Children and COVID-19

• Introduction: Kelly Dooley
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• Overview of Studies in Children at JHU
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• Remdesivir PK Study in Children
  • Allison Agwu, MD, ScM; Associate Professor, Pediatrics, Division of Infectious Diseases
• Convalescent Plasma in Children
  • Oren Gordon, MD; Senior Fellow, Pediatric Infectious Diseases

• Studies at All Children’s Hospital
• Neil Goldenberg, MD; Ph.D.; Professor and Director of Research
• Raquel Hernandez, MD; Assistant Professor, Pediatrics
• SARS-Co-V-2 Vaccines and Children
  • Kawsar Talaat, MD, Assistant Professor, Johns Hopkins Bloomberg School of Public Health
• Emergency Pediatrics During the COVID-19 Pandemic
  • Kemi Badaki-Makun, MD, Assistant Professor, Pediatric Emergency Medicine
• Cardiac Complications of SARS-CoV-2
  • Cedric Manlhiot, Assistant Professor, Pediatric Cardiology
Agenda Part 2- Pregnant Women and COVID

• Part 2: Pregnant Women and COVID
• COVID-19 in Pregnancy, an Overview plus Remdesivir in Pregnancy, A Clinical Trial
• Ahizechukwu Eke, MD, PhD, Assistant Professor, Maternal-Fetal Medicine, Department of Obstetrics and Gynecology
• Convalescent Plasma in Pregnancy
• Jeanne Sheffield, Professor of Obstetrics and Gynecology, Division Director, Maternal-Fetal Medicine
• Immune Responses to SARS-CoV-2 Infection in Pregnant Women
  • Irina Burd, MD, PhD, Professor of Obstetrics and Gynecology; Director, Integrated Research Center for Fetal Medicine

• Discussion & Q&A
Overview of SAR-CoV2 Infection in Children

Anna Sick-Samuels, MD, MPH
Assistant Professor of Pediatrics, Division of Pediatric Infectious Diseases
Associate Hospital Epidemiologist, Johns Hopkins Hospital
Epidemiology of SARS-COV-2 in Children

Symptom | Range
---|---
Asymptomatic | 16-19%
Fever | 48-59%
Cough | 39-56%
Rhinorrhea, nasal congestion | 7-20%
Myalgia | 14-19%
Sore throat | 14-18%
Headache | 3-13%
Tachypnea, dyspnea | 8-12%
Diarrhea | 7-10%
Nausea, vomiting | 2-9%
Abdominal pain | 6-7%
Fatigue | 5-8%
Rash | <1%

https://covid.cdc.gov/covid-data-tracker/#demographics
BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n385
Remaining Questions

• Are children at lower risk for getting infected if exposed?
  More asymptomatic/unrecognized infections?
  Just under-tested?
  Biologic reason? (eg, decreased viral entry)
  Protective immunity?

• Why do children have more mild manifestation?

• Are children less likely to transmit to others? Is this age or interaction dependent?
Multisystem Inflammatory Syndrome in Children (MISC)

- Post-infectious inflammatory illness ~4 weeks after infection
- Can rapidly progress to cardiac failure/hypotension
- 2/3 go to ICU
- 2-4% death
- Previously healthy, median age 8-9 years
- 2/3 among Hispanic or Black children
Unanswered questions

• What is the pathophysiology of MIS-C?
  — Different than Kawasaki’s disease?
  — Inform treatment options and timing
  — Long-term sequelae

• What are the risk factors for MIS-C?
  — Biologic risk factors
  — Protective immunity

• Can SARS-COV-2 infection lead to other aberrant immune responses or autoimmune conditions?
Overview of Studies of SARS-CoV-2 in Children at Johns Hopkins

Deborah Persaud, MD, Professor of Pediatrics, Division of Pediatric Infectious Diseases
Rationale for Pediatric Studies

- Epidemiology of coronavirus disease 2019 (COVID-19) in children is challenging to establish
  - High prevalence of asymptomatic infection

- Lower secondary attack rates in children compared to adults in household studies
  - May reflect lower testing in children and overall reduced exposure
  - May not reflect differences in biological susceptibility

- Shorter periods of shedding of infectious virus in children and less broad antibody responses than in adults
  - Make diagnosis challenging
  - Raise concerns for vaccine efficacy

Lower disease prevalence and low mortality raises ethical considerations for vaccine studies in children, especially with newer mRNA platforms
- Concerns around enhanced disease, such as MIS-C
- Long-term effects, and efficacy unknown

Knowledge gaps in:
- Epidemiology
- Immunopathogenesis
- Optimal therapies
- Immune responses
- Long-term consequences
- Risk-benefit assessment of mRNA SARS vaccine platform in children

Hyde Z, Differences in SARS-CoV-2 attack rates between children and adults may reflect bias CID 2021: in press
COVID-19 in Children

- Cohort Studies
- Vaccines and Seroprevalence Studies
- Immuno-pathogenesis
- Cardiac Complications and Long-term sequelae
- Biomarkers
- Social, economic, psychologic impact
- Therapeutics
• 15 y/o previously healthy adolescent girl (Dar’yana Dyson) who died within 4 days of presentation (Day 11 of an illness)

• Presented with one wk of epigastric pain, and anorexia, and two days of nasal congestion and rhinorrhea

• No sore throat, dyspnea, or cough

• Concern for intraabdominal process--transferred to JHU; COVID PCR test negative x 2

• Over the next 4 days, she developed worsening abdominal pain, fever, diffuse myalgias, and pleuritic chest pain → hypotension, increased work of breathing → hypoxemic respiratory failure → death over <12 hours.
  — Pro-BNP 8328 pg/mL
  — IL-6 239  CRP 30.9  ESR 118  WBC 37.5  B28%  ALC 750  PLT 280K

• SARS-CoV-2 IgG and IgA positive; 3rd COVID-19 PCR positive

• Diagnosis: Multisystem Inflammatory Syndrome Related to SARS-CoV-2
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CCPSEI Cohort Study

Nadine Peart, MD and Deborah Persaud, MD; Division of Pediatric Infectious Diseases
Background

• Immune dysregulation in adult patients with COVID-19 has been studied extensively in comparison to children; we are still understanding this disease in children

• Although SARS-CoV-2 in children is most often mild, the Multisystem Inflammatory syndrome in Children (MIS-C), associated with COVID-19 represents a severe phenotype in pediatric patients

• Better understanding of the immune dysregulation in this severe phenotype may inform risk stratification of those susceptible to severe disease and lead to earlier initiation and development of therapeutics to improve outcomes

JHU CCPSEI Cohort Study (Institution Supported) Principal Investigators: Lauren Sauer, MS; Paul Blair, MD (Adult Study); Deborah Persaud, MD (Pediatric Study)
Prospective cohort study nested within an adult study entitled “Clinical Characterization Protocol for Severe Emerging Infections”

**Interventions:**
- Prospective and/or retrospective sample collection
- Medical chart review for clinical, demographic and laboratory data
- Cytokine/chemokine profiles
- Quantitative viral RNA loads

**Outcomes/Measures:** Differences between those with and without MIS-C

As of March 8, 2021, there are 83 pediatric patients enrolled into the cohort
Results

FDR<0.05, p<0.05

Peart Akindele et al.; unpublished data, under review; 2021
Cytokine/chemokine Profiling: Andrew Karaba, MD, PhD, and Andrea Cox, MD, PhD
Regardless of age or MIS-C status, 2 cytokines correlated with female sex, FDR <0.25, p<0.05

There were 3 cytokines (★) that also showed a trend of being higher in female patients with MIS-C, FDR <0.25, p<0.05

Regardless of sex or MIS-C status, 1 cytokine correlated with age, FDR <0.025, p<0.05

Peart Akindele et al.; unpublished data, under review; 2021

CONCLUSIONS

SARS-CoV-2-infection in children leads to a distinct pattern of heightened cytokine/chemokine dysregulation with MIS-C compared to acute COVID-19, irrespective of age or sex
Remdesivir PK study in Children

Allison Agwu, MD ScM (Site PI)
Aleisha Collinson-Streng, RN (Senior Nurse Study Coordinator)
Remdesivir (RDV) in vitro activity against SARS-CoV-2

Mechanism of action: nucleotide prodrug intracellularly metabolized into analog of adenosine triphosphate inhibiting viral RNA polymerases; has broad activity against CoVs, and other viruses (filoviruses, paramyxoviruses)

Adult data: RCT showed superior to placebo in shortening time to recovery in adults hospitalized with COVID-19 and lower respiratory tract disease; shorter time to recovery (9-10 days vs. 15 days)

Overall safe in adults—up to 10 daily infusions

No data in children (potential for different PK among children)

Study considerations: While overall children do better with SARS-CoV-2, some may have significant disease and could benefit from administration

Therefore, higher risk children (hospitalized and needing intervention) selected as the target study population

(Sponsor: Gilead Sciences, Inc)(NCT04431453)

First prospective pediatric study on RDV among children 0-18 years
Parenteral administration
52 centers (US, UK, Italy, Spain)
Coordination between HIV Clinical Research Team, Peds ID, Critical Care, Pharmacy, and Pediatric Services
  • Significant off hours commitment

Preliminary results: JHU
• Number of participants: 4 (1 male, 3 females)
• Median age 5.5 years (4 months – 15 years)
• Comorbidities: immunodeficiency, chronic lung disease, genetic/chromosomal anomaly, muscular atrophy
• Median time from presentation to RDV: 2.5 days
• Duration of treatment: average 5 days
• Concomitant meds: 3/4 also received convalescent plasma, all received dexamethasone
• Overall study: 49/52 enrolled

Safety outcomes
• There were no SAEs (JHU); overall data unavailable

1 excluded:
  Not eligible (0)
  Did not give consent (1)

5 potential participants

4 enrolled and dosed

4 participants being followed for 30 days

At least 52 participants aged 0 days to < 18 years will be enrolled as described in the table below.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 12 years to &lt; 18 years and weight ≥ 40 kg</td>
</tr>
<tr>
<td>2</td>
<td>≥ 28 days to &lt; 18 years and weight ≥ 20 kg to &lt; 40 kg</td>
</tr>
<tr>
<td>3</td>
<td>≥ 28 days to &lt; 18 years and weight ≥ 12 kg to &lt; 20 kg</td>
</tr>
<tr>
<td>4</td>
<td>≥ 28 days to &lt; 18 years and weight ≥ 3 kg to &lt; 12 kg</td>
</tr>
<tr>
<td>5</td>
<td>≥ 14 days to &lt; 28 days of age, gestational age ≥ 37 weeks and weight at Screening ≥ 2.5 kg</td>
</tr>
<tr>
<td>6</td>
<td>0 days to &lt; 14 days of age, gestational age ≥ 37 weeks and birth weight ≥ 2.5 kg</td>
</tr>
<tr>
<td>7</td>
<td>0 days to &lt; 56 days of age, gestational age ≤ 37 weeks and birth weight ≥ 1.5 kg</td>
</tr>
<tr>
<td>8</td>
<td>&lt; 12 years and weight ≥ 40 kg</td>
</tr>
</tbody>
</table>

open cohorts
Convalescent Plasma in Children

Oren Gordon, MD; Senior Fellow, Pediatric Infectious Diseases
Safety and Pharmacokinetics of High-Titer Anti-SARS-CoV-2 Human Convalescent Plasma in High-Risk Children (NCT04377672)

- Human convalescent plasma has been used for infection prevention and treatment, including in children, for over a century (e.g., pneumococcus, measles, influenza, SARS).
- While little information was available at the initiation of the study (May 2020), data had accumulated since:
  - Administration of convalescent plasma has been demonstrated to be safe in adults.
  - One randomized, double-blind, placebo-controlled trial demonstrated significant benefit in preventing severe respiratory disease with administration of high-titer (>1:1000) convalescent plasma within 72 hours of symptom onset.
- On-going studies to test efficacy in adults: early outpatient treatment (NCT04373460; PI: David Sullivan) and prevention following high-risk exposure (NCT04323800; PI: Shmuel Shoham).

Rationale for Pediatric studies

- Convalescent plasma may be different in children:
  - Safety (ADE, allergic reaction, TACO, TRALI)
  - Pharmacokinetics (size and developmental stage may affect antibody distributing and elimination)
  - Potential alteration in endogenous immunological response due to convalescent plasma.
- Due to mild disease in children, a more than minimal risk intervention required some potential benefit.
- Therefore, high risk children were chosen as the target population.

Primary endpoint: Safety (Incidence of SAE)
Secondary objectives: Antibody PK and endogenous immune response

Safety and Pharmacokinetics of High-Titer Anti-SARS-CoV-2 Human Convalescent Plasma in High-Risk Children (NCT04377672)

- First prospective Pediatric study for COVID-19 convalescent plasma; Funded by the State of Maryland and Michael Bloomberg
- FDA IND (20185; April 2020) → study protocol shared on-line
- Formed a Pediatric COVID-19 convalescent plasma working group and multi-center registry

Safety outcomes
- No SAE reported in any participant
- Information from registry available for additional 33 children (17 males, 16 females, median age 14 years; range 0-19 years)
- No transfusion reactions reported there as well

PK analysis and modeling
- Transfer of multiple specific anti-SARS-CoV-2 antibodies
- Half-lives of anti-S and anti-RBD were 7-23 days, regardless of weight or age and within the expected range for IgG
- Since a “protective titer” in recipients is not well defined, the duration of potential protection remains unknown

Gordon et al., Unpublished data., 2021
Studies at All Children’s
The COVAC-TP Trial

PI: Anthony Sochet

Coordinating Site Investigators:
John Morrison, MD, PhD
Neil Goldenberg, MD, PhD
COVID-19 Anticoagulation in Children – Thromboprophylaxis (COVAC-TP): National (U.S.) Phase 2 Clinical Trial

- Supported via a COVID Rapid Response Grant from the Johns Hopkins All Children’s Foundation Institutional Research Awards Program

Assistant Prof, JHU SOM ACCM, (based on JHAC campus): Since 2016
Fellowship: Children’s National (D.C.)
Masters in Clinical Research: GWU
March 2020 – First recognition of clotting complications in patients hospitalized for COVID-19

• Within 3 weeks:
  — Protocol developed & submitted via a multidisciplinary team based in JHAC ICTR
  — Grants developed & submitted
    > U01 Supplement (Goldenberg)
    > JHAC Foundation IRAP (Sochet)
  — FDA IND waiver filed & granted
  — Consortium LOS/LOI obtained from 15 centers (leveraged existing U01 trial network)
March 2020 – Trial Design

• **Agent**: Lovenox

• **Dosing**: 0.5mg/kg sc q12h

• **Primary endpoint**: Safety (ISTH-defined bleeding: major + clinically-relevant non-major)

• **Secondary endpoint**: Dose requirements (mg/kg) by age group (to achieve plasma anti-Xa activity levels in target range)

• **Exploratory endpoint**: Efficacy (ISTH-defined venous thromboembolism [VTE] or VTE-related death)
Enrollment began at JHACH
Activated 9 of 15 sites
JHAC ICTR served as:
— Clinical Coordinating Center
— Data Coordinating Center
— Central Biorepository (CAP-accredited pediatric biorepository)

April 2020 – Trial opened

| Children’s Hospital Los Angeles |
| Children’s of Alabama |
| Lurie Children’s Hospital |
| Children’s Medical Center of Dallas |
| Johns Hopkins Hospital & Children’s Center |
| Johns Hopkins All Children’s Hospital |
| Children’s Hospital of New Orleans |
| Children’s Hospital of Atlanta |
| Rady Children’s Hospital |
| Boston Children’s Hospital |
| Akron Children’s Hospital |
| Children’s Hospital of Michigan |
| Children’s Hospital Pittsburgh |
| Rush University Medical Center |
| Cohen Children’s Medical Center |
| UC Davis Children’s Hospital |
• Enrollment is ~80% complete
• Steering Ctte, Clinical Endpoint Adjudication Committee, and Data and Safety Monitoring Committee have met regularly
• Timely data collection in REDCap with Study Quality Monitoring Reports produced monthly by the DCC in JHAC ICTR
• Serial plasma biospecimens collected on all patients to date, locally stored at -80C, and batch-shipped to central biorepository at JHACH
The Impact of COVID-19 on Families of Young Children in the PREDICT Cohort

Raquel G. Hernandez MD MPH
Sara Johnson PhD
Prospective Research on Early Determinants of Illness and Children’s Health Trajectories
Specific Aims

• **Aim 1:** Describe the prevalence of COVID-19 symptoms, testing, and treatment among families with young children
  — Characterize variation by socioeconomic status, maternal pre-pandemic health status, and health insurance status

• **Aim 2:** Evaluate the impact of COVID-19 on economic conditions, family routines, family functioning, psychosocial stress, and food access among families with young children.
  — Using primary care medical records, characterize child health status and healthcare utilization before and during the pandemic.
COVID Impact: Early Results

- n=194 mothers (203 children)
- 11% of mothers had a positive COVID test, 45% had been tested
- 6% of children had a positive COVID test and 17% had been tested
- 63% of mothers reported COVID impact in 8 of 9 domains
  - racial/ethnic minority participants had greater impact than whites, p<0.03
- Financial stress scores ↑ 48% pre-pandemic to pandemic, p<0.0001
- Anxiety symptom scores ↑ 17% pre-pandemic to pandemic, p<0.0001

- Factors associated with increased COVID impact:
  - Not living with the father in pregnancy, financial stress in pregnancy
- Factors not associated with COVID impact:
  - Essential employee status, education level, anxiety symptoms in pregnancy
Acknowledgements

• JHAC Foundation Institutional Research Grant
• JHU Alliance for a Healthier World
• Collaborators: Drs. Heather Volk, Rachel Thornton, Nakiya Showell, Sharon Ghazarian
• Co-PIs: S. Johnson & N. Goldenberg who pioneered building of the study and funding the work
• Study coordinators: S. Flanagan, L. Dallas for their ongoing efforts
SARS-Co-V-2 Vaccines and Children

Kawsar Talaat, MD, Assistant Professor, Johns Hopkins Bloomberg School of Public Health
SARS-CoV2 Epidemiology And Response in Children

• Study of SARS-CoV-2 infection, transmission, and immunity in households with 1 or more children under age 5

• CDC-funded, complements 4 other U.S. household studies that focus on older children and adults

• Weekly nasal swabs for 8 months; weekly and monthly questionnaires
  — SARS-CoV-2 PCR (Marshfield RI)
  — SARS-CoV-2+ to be tested for genetic variants
  — Swabs from ill children <5 to be tested by multiplex PCR for other pathogens in Ruth’s lab

• Monthly oral swabs; + weekly for 8 weeks in SARS-CoV-2+
  — Tested for SARS-CoV-2 IgG to spike and internal proteins in Chris Heaney’s lab

• Sera collected at enrollment and at 4 and 8 months post enrollment
  — SARS-CoV-2 IgG to spike and internal proteins; microneut for IgG+ specimens

• 175 households, 682 individuals, 255 children < 5 years enrolled Nov 2020-Feb 2021
  — At enrollment: ~50% of children under 5 attend daycare outside the home; 25% of adults work outside the home; 75% of households have one or more household members attending work/school/childcare outside the home
  — Study compliance to date is high:
    ▪ 98% of weekly nasal swabs and 92% of oral swabs collected and received on time; 99% of weekly and 97% of monthly surveys completed

• To date, 9 households and 23 individuals SARS-CoV-2 PCR+
  — Only 1 of 9 households had all household members infected

• More to come!
Evaluation of the Pfizer/BioNTech mRNA Vaccine in Children 5-11 years of age

• Phase 1: Starting late March/Early April
  —Open Label, Dose Finding up to 48 children across 4 sites
  —Safety, Tolerability, and Immunogenicity
  —Start with 10 mcg/dose going up or down based on tolerability, immunogenicity

• Expanding to Phase 2/3 in June
  —Placebo controlled, multi-site. Randomized 2:1
  —Dose from Phase 1
  —Safety, immunogenicity
  —Unblinded at 6 months- placebo recipients invited to receive vaccine

• Anticipated Protocol amendment to expand groups to age 2-5 years and 6mo-2 years
Emergency Pediatrics During the COVID-19 Pandemic

Kemi Badaki-Makun, MD, Assistant Professor, Pediatric Emergency Medicine
Home Activities & Injury
2,011 respondents, weighted to adult US pop

### Daily Activities
- 23% began WFH
- 33% home improvement projects
- 15% alcohol
- 48% home cleaning & maintenance
- 31% exercise; 20% active recreation
- 13% supervising of kids’ sports or play

### Injuries in HH
- 26% of HH had someone injured:
  - 32% falls
  - 20% cut
  - 9% burns
- 11% of HH had medication ingestion
- 6% of HH had household project ingestion

### Medical Care
- 34% in person medical care
- 12% virtual or phone visit

- **DID NOT SEEK CARE**
  - 42% not serious enough
  - 7% COVID concerns

- 25% thought very or somewhat likely they would get infected
- 83% thought it would be very or somewhat serious

### Additional Information
- 68% time spent at home from COVID

High Acuity Traumas
2020 vs. 2017-19

Figure 1: High Acuity Traumas as a Proportion of all Emergency Department Visits
## High Acuity Traumas
### 2020 vs. 2017-19

<table>
<thead>
<tr>
<th>Trauma Type</th>
<th>2017-2019 Mean</th>
<th>95% Confidence Interval</th>
<th>2020 Count</th>
<th>Percent Change (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assaults</td>
<td>6.7</td>
<td>5.2–8.2</td>
<td>10</td>
<td>+ 49.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor Vehicle Accidents</td>
<td>77.3</td>
<td>76.3–78.3</td>
<td>63</td>
<td>- 18.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Falls</td>
<td>68.7</td>
<td>66.7–70.7</td>
<td>51</td>
<td>- 25.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drowning</td>
<td>8.7</td>
<td>7.8–9.5</td>
<td>6</td>
<td>- 31.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Child Abuse</td>
<td>8.7</td>
<td>7.4–9.9</td>
<td>16</td>
<td>+ 83.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal Attack</td>
<td>5.7</td>
<td>4.1–7.2</td>
<td>5</td>
<td>- 12.3</td>
<td>=0.38</td>
</tr>
</tbody>
</table>
Identifying MIS-C
Role of the Monocyte Distribution Width (MDW)

Identifying MIS-C
Role of the Monocyte Distribution Width (MDW)

Cardiac Complications of SARS-CoV-2

Cedric Manlhiot, Assistant Professor, Pediatric Cardiology
A data science approach to identify and manage Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2 infection and Kawasaki disease in pediatric patients
C. Manlhiot (NPI), B.W. McCrindle, N. Dahdah, T. Giglia, S. Kutty
Study rationale and objectives

- MIS-C and KD have overlapping features, significance of overlap still unknown
- COVID/MIS-C is new, few predictive algorithms to use as part of CDSS
- But, KD has been extensively studied and predictive algorithms have been developed
- Can we retrain algorithms designed for KD in patients with COVID/MIS-C?
- Will use 3 classes of algorithms previously designed for KD for use in COVID/MIS-C:
  - 1) Diagnosis and clinical identification
  - 2) Optimization and personalization of therapy
  - 3) Prediction of refractory diseases/severe complications
- CDSS designed to be useful for any patient along the KD to MIS-C clinical spectrum
Phased approach to algorithm development

Phase 1: Data exploration and algorithms development
- Collect data for training dataset (N=450, 1:1:1 MIS-C:COVID:KD)
- Clinical profiling of patient cohorts
- Re-train previously developed algorithms in new populations

Phase 2: Algorithms expansion and performance evaluation
- Collect data for validation dataset (N=450, 1:1:1 MIS-C:COVID:KD)
- Add inflammatory/cardiac biomarkers to the algorithms
  - Focusing on biomarkers that are usually available in standard clinical labs
- Estimate performance metrics of algorithms in internal validation

Phase 3: Algorithms validation, implementation and clinical utility
- Collect data for external validation dataset (N=450, 1:1:1 MIS-C:COVID:KD)
- Add local and global epidemiology data to the diagnostic algorithm
- Determine performance metrics of algorithms in external validation
- Algorithm packaging, deployment and certification in standalone CDSS
- Shadow testing to validate implementation strategy
- Assessment of clinical utility and human factor evaluation
Performance sites and key people

23 clinical enrollment sites (17 USA, 6 international)

Benjamin T. Barnes, Johns Hopkins University, Baltimore MD
Jean Ballweg, Children’s Hospital & Medical Center, Omaha NE
Nagib Dahdah, CHU Sainte-Justine, Montreal QC (Co-PI)
Prasad Deepa, Banner Children’s at Desert, Mesa AZ
Audrey Dionne, Boston Children’s Hospital, Boston MA
Matthew Elias, Children’s Hospital Philadelphia, Philadelphia PA
Ashraf Harahsheh, Children’s National Hospital, Washington DC
Supriya Jain, Maria Fareri Children’s Hospital, Nyack NY
Manaswita Khare, Rady Children's Hospital/UCSD, San Diego CA
Dan Mauriello, John's Hopkins All Children’s, St. Petersburg FL
Brian W. McCrindle, Hospital for Sick Children, Toronto ON (Co-PI)
Misra Nilanjana, Cohen Children's Medical Center, New York NY
Todd T. Nowlen, Phoenix Children’s Hospital, Phoenix AZ
Michael Portman, Seattle Children's Hospital, Seattle WA
Geetha Raghuveer, Children’s Mercy Hospital, Kansas City, MO
Kristen Sexson Tejtul, Texas Children’s Hospital, Houston TX
Jackie Szmuszkovicz, Children’s Hospital Los Angeles, Los Angeles CA
Deepika Thacker, Nemours A.I. DuPont Hospital, Newark DE
Dongnhan Truong, Primary Children’s Hospital, Salt Lake City, UT
Sundaram Balasubramanian, Kanchi Kamakoti Childs, Chennai, India
Elisa F. Cooke, Hospital Universitario 12 de Octubre, Madrid, Spain
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Mona El-Ganzoury, Ain Shams University, Cairo, Egypt

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Martha Rolland
Patricia Walter
Data management
Tanveer Collins
Bailey Bernknopf
Data analysis
Kyle Runeckles
Brigitte Mueller
Clinical lead
Therese Giglia, CHOP (PI)

Lead analytics
Cedric Manlhiot (NPI)
Lead imaging
Shelby Kutty, JHU (PI)
Lasya Gaur, JHU
Lead biomarker
Allen Everett, JHU
Research manager
Love Ko
Observational study embedded in the IKD Registry

IKDR registry:
- KD
- COVID
- MIS-C

Patient enrolled in data science study

Core data collection

Patient enrolled in IKDR CAA registry

CAA

No CAA

Yearly data update (open-ended)

IKDR DCC

Data science study protocol

Consent (or waiver)

Blood sampling

Ancillary data collection

JHU biomarker laboratory

Discharge/1 year data collection

submitted by site

Data validation by DCC

JHU core imaging lab

Echo/MRI

JHU CV-Ai2 analytics

NIH RADx DCC + data archives
Anticipated results

- Algorithms meet minimal standards for performance and utility
- Functional prototype of the CDSS shown above at the end of phase 2
- Clinically-approved, deployment ready platform of the CDSS at the end of phase 3
COVID-19 in Pregnancy, an Overview plus Remdesivir in Pregnancy, A Clinical Trial

Ahizechukwu Eke, MD, PhD, Assistant Professor, Maternal-Fetal Medicine, Department of Obstetrics and Gynecology
Clinical Course of COVID-19 in Pregnancy

- Overall spectrum of COVID-19 symptoms similar in pregnant and nonpregnant women.

- Early data from systematic review of studies to April 29, 2020, suggested pregnant women had similar COVID-19 course as nonpregnant adults[1]

- However, several recent studies demonstrated increased rate of hospitalizations, ICU care, and mechanical ventilation, but not death, in pregnant women vs age-matched nonpregnant controls[2-4]

<table>
<thead>
<tr>
<th>Clinical Outcome, % (95% CI)</th>
<th>Total (N = 538*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe disease</td>
<td>15.3 (11.1-20.8)</td>
</tr>
<tr>
<td>Critical disease</td>
<td>1.4 (0.5-4.1)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>3.0 (1.6-5.9)</td>
</tr>
</tbody>
</table>

*China, n = 420; US, n = 76; Europe, n = 42.

## FDA Approval for Remdesivir: Use in Special Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>No adequate and well-controlled studies. No pharmacokinetic studies</td>
</tr>
<tr>
<td>Nursing mothers</td>
<td>No information regarding remdesivir in human milk, effects on breastfed infants, or effects on milk production; in animal studies, remdesivir and metabolites are detected in the nursing pups of mothers given remdesivir, suggesting the presence of remdesivir in milk</td>
</tr>
<tr>
<td>Pediatric</td>
<td>Safety and efficacy for treating COVID-19 have not been assessed in pediatric patients younger than 12 yrs or weighing less than 40 kg; FDA EUA in effect for pediatric patients younger than 12 yrs or weighing less than 40 kg</td>
</tr>
<tr>
<td>Geriatric</td>
<td>Clinical experience has not identified differences in responses between elderly and younger patients; no dosage adjustment required; should be monitored closely for hepatic, renal, and cardiac function</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Remdesivir PK not evaluated in patients with renal impairment; not recommended patients with eGFR &lt; 30 mL/min</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Remdesivir PK not evaluated in patients with hepatic impairment; perform hepatic testing prior to starting and while receiving remdesivir</td>
</tr>
</tbody>
</table>
Remdesivir PK Study in women – IMPAACT 2032

• **Purpose:** To describe the pharmacokinetic (PK) properties and safety of remdesivir (GS-5734TM) (RDV) administered to pregnant and non-pregnant women with COVID-19.

• **Design:** Phase IV, prospective, open label, non-randomized opportunistic PK study

16 participating centers in 9 US States and PR
Study Population and sample size: There are 2 arms: Pregnant and non-pregnant women of childbearing potential hospitalized and receiving RDV for treatment of COVID-19.

Arm 1: Pregnant women
Target enrolment of 20 pregnant women with evaluable PK data

Arm 2: Non-Pregnant women
Target enrolment of 20 non-pregnant women with evaluable PK data
Overview of Study Design

**Arm 1**
- Pregnant Women Hospitalized with COVID-19
  (Target 20 PK evaluable)

**Arm 2**
- Non-Pregnant Women Hospitalized with COVID-19
  (Target 20 PK evaluable)

**Pre-Infusion**
(48 hours pre-first infusion)

**RDV Infusions**

**Safety Follow-up**
(48-Hours, 7-Days, 28-Days Post-Last Infusion)

**Arm 1 only: Delivery**

Safety Evaluations: Clinical and Laboratory Data Collection (Chart Abstraction/Remote Visits)

- Intensive PK Sampling (3rd, 4th or 5th infusion)
- Breast milk collection (lactating women who consent only)
- Single PK Sampling (2nd – 5th infusions)*
  *(Single PK sampling will not occur on day of intensive PK sampling)

- Single PK Sampling (48-Hours only)*
  *(Only for women still hospitalized)
- Breast Milk Collection (48-Hours only)*
  *(Only for pregnant women who received RDV within 5 days prior to delivery)
- Single PK Sampling (maternal and cord blood)*
  *(Only for pregnant women who received RDV within 5 days prior to delivery)

*Delivery visit may occur during infusions or safety follow-up.
Remdesivir PK Study in women

• **Drug under study:** Participants will be administered RDV intravenously once daily for up to 10 days per clinical care.

• **Study Duration:**
  — Approximately 15 months total
  — Accrual is expected to be completed within approximately 6 months from first enrollment
  — Enrolled women in Arm 1 will be followed for 4 weeks after the last RDV infusion or through delivery, whichever comes later. Enrolled women in
  — Arm 2 will be followed for 4 weeks after the last RDV infusion.

• **Status:** Open to accrual at JHH

• **Contact:** aeke2@jhu.edu
Convalescent Plasma in Pregnancy

Jeanne Sheffield, Professor of Obstetrics and Gynecology, Division Director, Maternal-Fetal Medicine
Compromised Use of Remdesivir in Pregnant Women With Severe Coronavirus Disease 2019

- 3/21/2019-6/13/2019 86 hospitalized pregnant women with PCR confirmed disease and oxygen saturations <94%.
- Well tolerated, low AEs
- No safety signals

![Graphs showing clinical outcomes in pregnant and postpartum women treated with remdesivir at day 28. Mechanical ventilation includes invasive ventilation by endotracheal tube or tracheostomy. Blue shading indicates improvement from baseline oxygen support. *P* values calculated from BL/D support groups; MV includes invasive ventilation by endotracheal tube or tracheostomy. Abbreviations: BL, baseline; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; NIPPV, noninvasive positive pressure ventilation; O₂, oxygen.](image-url)
Human Coronavirus Immune Plasma (HCIP) and Use in Pregnant Patients with Sars-CoV-2 infection David Sullivan PI

• Convalescent plasma is not contraindicated in pregnancy
• Randomized double-blind Phase 2 trial
  — Efficacy and safety of HCIP compared to control plasma
  — Endpoints: hospitalization, death, duration or symptoms and viral shedding, antibody titers
• Positive RNA or antigen test and symptoms
• Outpatient only
HCIP Study

• This is not a pregnancy study. However, due to the known risk of severe disease and death in pregnant women and the lack of contraindication of plasma therapy in pregnancy, pregnant women are being enrolled using the same inclusion and exclusion criteria.
COVID-19 in Pregnancy: Implications of dysregulated maternal immunity

Irina Burd, MD, PhD
Professor and Director
Integrated Research Center for Fetal Medicine
Maternal Fetal Medicine, Gynecology and Obstetrics
Johns Hopkins University
Pregnancy alters IL-1β expression and anti-viral antibody responses during SARS-CoV-2 infection

Main findings:

• Pregnant women who delivered <14 days after positive SARS-CoV-2 test expressed more IL1β mRNA in their blood compared to pregnant women who were uninfected or delivered >14 days after a confirmed test.

• Pregnant women with confirmed infection had lower anti-spike-receptor binding domain IgG titers and were less likely to have detectable neutralizing antibodies compared to non-pregnant women.

• Protein concentrations of placental FcRn, a receptor essential for maternal transfer of antibodies to the fetus were not affected by SARS-CoV-2 infection during pregnancy.
Pediatric Follow Up of the Cohort

**Co-PIs**
- Irina Burd, MD, PhD
- W. Christopher Golden, MD
- Robert Yolken, MD

**Cohort**
- 100 enrolled patients
  - Maternal blood
  - Cord blood
  - Placenta
  - Neonatal Blood
  - Stool
  - Breast milk
  - Neurologic follow up with Kennedy Krieger
Pregnancy Outcomes In SARS-CoV-2 Epidemic (POISE): Maryland State Study

- Collaboration with University of Maryland
- Capture all of COVID-19 pregnancy outcome data in Maryland
- BEAD core
- Findings will be presented at the Society for Reproductive Investigations Annual Meeting in July 2021
Thank you

COVID-19 Clinical Research Center
https://ictr.johnshopkins.edu/covid-research-center/town-halls/

COVID19ResearchCtr@jhmi.edu