ECHO-Bateman Horne Series
September 20, 2022

Pediatric Long COVID

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Disclosures and Conflicts of Interest

• Eryka Pawlak: None

• Dongngan Truong:
  • Grant Support: NIH
  • Co-PI on research that receives funding from NHLBI Pediatric Heart Network and Pfizer
Objectives

• Understand pediatric long COVID in the spectrum of other post-viral syndromes
• Better understand pediatric long COVID
  • Prevalence
  • Who gets pediatric long COVID
  • Clinical symptoms/manifestations
• Inform of Primary Children’s Hospital Long COVID Navigation Clinic
Post-Acute Sequelae of COVID-19 (PASC)/Post COVID Syndromes

• New or persistent symptoms after the acute COVID-19 infection
• Pediatric PASC
  • Multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C)
  • Long COVID
• Much less data on pediatric long COVID than
  • MIS-C
  • Adult long COVID
Long COVID vs Other Pediatric Post-Viral Sequelae

• The concept of post-viral syndromes and persistent sx is not new to peds

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Chronic fatigue</th>
<th>Lungs</th>
<th>Heart</th>
<th>Kidneys</th>
<th>Immune system</th>
<th>Brain</th>
<th>Cancers</th>
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<td>−</td>
<td>−</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
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For patients’ experience refer to Box 1, for literature details refer to the Supplementary Box.
Differences Between Peds/Adult COVID/Long COVID

• Most children and adolescents had mild disease (some asymptomatic)
  • Most were not hospitalized with COVID-19, even less in ICUs
• Children were/are less likely to be tested for COVID-19 than adults, even when testing was more widely available
  • Waning antibodies for testing can also be hard to interpret in dx long COVID
• <18 year old population encompasses wide spectrum of development
• Reliance on parents/other caregivers for care, symptom evaluation
• Much of current and future research will most likely focus on adults
  • Treatment strategies
Differences Between Peds/Adult COVID/Long COVID

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  • Most were not hospitalized with COVID-19, even less in ICUs
• Children were less likely to be tested for COVID-19 than adults, even when testing was more available
  • Waning antibodies for testing can also be false
• <18 year population encompasses a wide spectrum of development
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  • Treatment
Limitations to Pediatric Long COVID Research

• Lack of standard definition in research (and clinically)
  • No specific pediatric definition
  • Varying duration of symptoms, typically 4-12 weeks post acute infection
• Inclusion of children without confirmed SARS-CoV-2 infection
• Variable follow-up times

• WHO case definition:
  “Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis... Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.”

Limitations to Pediatric Long COVID Research

- Reliance on self- or parent-reported sx$s
  - Often without clinical assessments
  - No standardized testing assessment
- Absence of control groups
- Denominators are unknown
- Bias
  - Selection
    - Those affected more likely to respond
    - Higher SES with access to apps and internet
  - Non-response
  - Recall
Prevalence

• Prevalence of pediatric long COVID has been highly variable
• Early data suggested that the prevalence of long COVID may be >50%
• Subsequent studies note this is more likely up to about 4-6%
• Accurate determination plagued by limitations


<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Study</th>
<th>Age (yr)(^a)</th>
<th>Timing</th>
<th>Cases</th>
<th>Controls</th>
<th>Prevalence of patients with persisting symptoms</th>
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<tbody>
<tr>
<td>Blankenburg</td>
<td>Germany</td>
<td>CS</td>
<td>median 15 (14-16)</td>
<td>nr</td>
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<td>Miller</td>
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<td>PCS</td>
<td>nr, 517</td>
<td>4w</td>
<td>8/174</td>
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<td>5% p=0.009</td>
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<td>PCS</td>
<td>median 13 (10-15)</td>
<td>4w</td>
<td>77/1734</td>
<td>15/1734</td>
<td>4% p=0.0001</td>
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<td>Radtke</td>
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<td>PCS</td>
<td>median 11 (nr)</td>
<td>4w</td>
<td>10/109</td>
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<td>range 11-17</td>
<td>12w</td>
<td>2038/3065</td>
<td>1993/3739</td>
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<td>nr</td>
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<td>Norway</td>
<td>PCS</td>
<td>median 8 (6-12)</td>
<td>5m</td>
<td>2/18</td>
<td>nr</td>
<td></td>
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<td>Brackel</td>
<td>Netherlands</td>
<td>CS</td>
<td>median 13 (9-15)</td>
<td>nr</td>
<td>89</td>
<td>nr</td>
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<tr>
<td>Buonsenso</td>
<td>UK, USA</td>
<td>CS</td>
<td>mean 10 (3.8)</td>
<td>4w</td>
<td>510</td>
<td>nr</td>
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<td>Buonsenso</td>
<td>Italy</td>
<td>CS</td>
<td>mean 11 (4.4)</td>
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<td>Osmanov</td>
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<td>PCS</td>
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<td>5m</td>
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<td>16w</td>
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</table>

\(^a\) mean (SD), median (interquartile range), or range;
\(^b\) median 112d after infection, range 33-410d
\(^c\) median 163d after infection, SD 114d
\(^d\) mean 191d after infection, SD 17d

Studies with controls

Studies without controls
Pediatric Populations at Risk

• Factors that have been associated with long COVID development in <18 yo
  • Older age
  • Female sex
  • PMHx of allergic diseases
  • Worse pre-COVID physical or mental health
  • In those hospitalized, longer hospitalization correlated with >severe, persistent sxs
Symptoms

- Fatigue and malaise (general and post-exertional)
- Headaches
- Brain fog, attention problems
- Sleep disturbance
- Tachycardia and palpitations
- Chest pain
- Dysautonomia
  - POTS
  - Orthostatic intolerance
- Nausea*
- Abdominal pain*
- Rash
- Depression
- Anxiety
- Shortness of breath
- Chronic cough
- Fevers

Pediatric Long COVID vs. Myalgic Encephalitis/Chronic Fatigue Syndrome

• Overlap of symptoms
  • Fatigue, post-exertional malaise, sleep disturbance, cognitive impairment, lightheadedness

• Cerebral blood flow reductions during upright posture

• Females>males

• No diagnostic test

• Sxs management is focus of tx

• BUT Dx ME/CFS requires 6 mos sxs
  • Separate entity vs. trigger?

“Lilly Klontz, age 16, from OK, created this artwork in response to a contest prompt asking participants to depict how having ME/CFS makes people feel.” https://www.parentcenterhub.org/me-cfs/
Long COVID symptoms and duration in SARS-CoV-2 positive children — a nationwide cohort study

Luise Borch¹ • Mette Holm² • Maria Knudsen³ • Svend Ellermann-Eriksen⁴ • Soeren Hagstroem⁵,⁶

- Denmark (<18 yo): 37,522 COVID PCR+ vs. 78,037 controls (not tested +)
  - 44.9% (N=16,836) vs. 21.3% (16,642) response rates (cohorts: 15,041 vs. 15,080)
  - 0-5 yo: 14.8% COVID+ vs. 17.6% controls had sxs >4 weeks (p=0.001)
  - 6-17 yo: 28% vs. 27.2% had sxs >4 weeks (p=0.02)

Panel B

Long Covid symptoms, age 0-5 years

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Risk difference (95% CI), P-value</th>
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</thead>
<tbody>
<tr>
<td>Respiratory problems</td>
<td>0.00 (-0.00; 0.01), P = 0.41</td>
</tr>
<tr>
<td>Nausea</td>
<td>-0.00 (-0.01; 0.00), P = 0.13</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>0.00 (0.00; 0.01), P = 0.00</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>0.00 (-0.00; 0.00), P = 0.76</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>0.01 (0.01; 0.02), P = 0.00</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>0.01 (0.01; 0.01), P = 0.00</td>
</tr>
<tr>
<td>Joint pain</td>
<td>0.00 (-0.00; 0.01), P = 0.05</td>
</tr>
<tr>
<td>Headache</td>
<td>0.01 (0.00; 0.01), P = 0.04</td>
</tr>
<tr>
<td>Fever</td>
<td>-0.02 (-0.03; -0.02), P = 0.00</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.05 (0.04; 0.05), P = 0.00</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.00 (-0.00; 0.00), P = 0.67</td>
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<tr>
<td>Diarrhea</td>
<td>-0.01 (-0.02; -0.01), P = 0.00</td>
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<tr>
<td>Cough</td>
<td>-0.06 (-0.07; -0.05), P = 0.00</td>
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<tr>
<td>Concentration difficulties</td>
<td>-0.01 (-0.02; -0.01), P = 0.00</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.00 (-0.00; 0.00), P = 0.08</td>
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</tbody>
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Panel C

Long Covid symptoms, age 6-17 years

Respiratory problems
Nausea
Muscle weakness
Muscle pain
Loss of taste
Loss of smell
Joint pain
Headache
Fever
Fatigue
Dizziness
Diarrhea
Cough
Concentration difficulties
Chest pain

Risk difference (95% CI), P-value

0.03 (0.03; 0.04), P = 0.00
-0.02 (-0.02; -0.01), P = 0.00
0.02 (0.01; 0.02), P = 0.00
-0.01 (-0.02; -0.01), P = 0.00
0.10 (0.09; 0.10), P = 0.00
0.12 (0.12; 0.13), P = 0.00
-0.01 (-0.02; -0.01), P = 0.00
-0.02 (-0.03; -0.01), P = 0.00
-0.01 (-0.01; -0.00), P = 0.00
0.05 (0.04; 0.06), P = 0.00
0.02 (0.02; 0.02), P = 0.00
-0.01 (-0.01; -0.01), P = 0.00
-0.01 (-0.01; -0.01), P = 0.00
-0.09 (-0.09; -0.07), P = 0.00
0.01 (0.01; 0.01), P = 0.00
Comparison of mental health outcomes in seropositive and seronegative adolescents during the COVID19 pandemic

Judith Blankenburg¹, Magdalena K. Wekenborg², Jörg Reichert³, Carolin Kirsten¹, Elisabeth Kahre¹, Luise Haag¹, Leonie Schumm¹, Paula Czyborra¹, Reinhard Berner² & Jakob P. Armann³

- 1560 teens (median age 15 yo)
- 188 (12%) seropositive vs. 1365 (88%) seronegative (serial testing)
- 12 question long COVID-19 survey from Symptom Checklist-90-R, the Somatic Symptom Scale, and questionnaire about stress/stress management during March/April 2021 visit (SchoolCOVID19 study)

Research is Underway

• [https://recovercovid.org/](https://recovercovid.org/)
Primary Children’s Long COVID Navigation Clinic
Rationale

• Anticipated the need within the pediatric population
• Lots of questions from families/providers if a long-COVID clinic would be established for children/adolescents

• Unknowns and considerations
  • How great will the need be, and how can we adapt quickly as the need becomes clearer?
  • Navigation clinic vs. multidisciplinary subspecialty clinic?
  • Separating long-COVID from other entities?

• Major aim: To support children and adolescents with long COVID and help them return to functional status
  • Return to school and activities
Care Team

Eryka Pawlak, NP-C
Clinic Nurse Practitioner (0.5 FTE)

Dongngan Truong, MD, MS
Medical Director

Shaylnn Mackie, MA PRN

Corrine Espinoza, Psychologist (0.1 FTE)
• Starting October 2022
PCH Long COVID Navigation Clinic

• Opened in mid April 2022
• Help to evaluate for alternative diagnoses
• Refer as needed to specialist care and assist in the management of symptoms

• **Telehealth clinic** that can virtually see patients <18 years old in Utah, Nevada, Idaho and Montana
  • We hope to see patients from Wyoming soon

• Patients need to be referred by their PCP, 2 ways:
  • Electronically through iCentra
  • Via fax at 385-297-2750
PCH Long COVID Navigation Clinic

- Half-day clinic a week
  - 60 minute appointments
- We use WHO definition for clinic (though no one has been turned away)
- Red Cap Survey, to be completed ahead of time
  - Past medical & surgical history
  - Family history
  - COVID 19 history with current symptoms
  - Functional status and behavioral health
    - Functional disability index
    - SSS8
    - Mental fatigue screening
    - Day of clinic PHQ-9 depression screening
Who We Have Seen

• Total new patients seen in clinic: 43
• Follow-ups: 10
• Female: 31 (72%)
• Age range: 5 months to 17 years
• Most common symptoms: fatigue, orthostatic intolerance/dysautonomia symptoms, pain-abdominal, chest, muscle/joint, and headaches, brain fog, sleep problems, exercise intolerance, anxiety & depression
• Most common referrals we have made
  • Integrative Medicine, Behavioral Health, Physical Therapy, Cardiology (for Orthostatic Intolerance Symptoms)
Next Steps

• Broaden our reach to Wyoming
• Website, getting the word out
• Working on physical space to see some patients in-person
• Hoping for future collaborations with the new PAUSE clinic
  • Similar goals
  • Similar patient populations
  • Resource sharing
  • Alignment of treatment modalities and practices
  • Uniform education
A Typical Scenario

• 17 yo presented 5/12/2022 (COVID-19 infection 11/2020)
• Initial sxs: Headache; tested because father texted positive
  • No hospitalization, no meds; no persistent sxs
• 2\textsuperscript{nd} COVID infection: Sxs around 2/1/2022, Ab testing + 2/26/2022
  • Fatigue, headaches; resolved then restarted
• No COVID-19 vaccination
• Sxs at initial appt
  • Brain fog, memory loss, confusion, difficulty concentrating, dizziness, depression, anxiety, problems sleeping, heart palpitations, racing heart- followed by dizziness then passing out on a regular basis, shortness of breath, generalized weakness without focal weakness, fatigue, abdominal pain, and nausea
  • Worst sxs: Tachycardia, syncope, fatigue
Initial Questionnaire Results

**Functional Disability Inventory** = 36 (severe)

**Sleep Disturbances** = 27 (high)

**PHQ Depression Scale 2a90**
- 4/27/22 (Parent): 19 (mod severe) No thoughts of harming self or wanting to be dead
- 5/12/22 (Patient): 16 No thoughts of harming self or wishing to be dead

**Parent Pain Pcs** = Total score 0

**Checklist Individual Strength- Mental Fatigue** = 15 (moderate)

**Somatic Symptom Scale (SSS8)** = 17 (very high)

9 out of 10 debilitation score

25% baseline mood

0% baseline activity participation

50% baseline for school function
Prior Work-up and Referrals by PCP

- Normal labs: Celiac Disease Dual Antigen Screen, CRP, CMP, ESR, CBC (except for elevated lymphocytes at 69%), ferritin, free T4, TSH
- Strep A cx: NEG
- SARS COV2 IgG Antibody: Positive
- Referral to Behavioral Health
What We Recommended

• Testing
  • Labs: Vitamin B12, Vitamin D levels (never obtained)
  • ECG: Normal

• Referrals
  • Cardiology: dx’d with orthostatic intolerance
    • Increase fluids and salt intake
    • Regular exercise/stretching if tolerated
    • If sxs not improving in 2-3 months, consider ivabradine
  • Behavioral Health
  • Integrative Medicine

• Symptom management recommendations
  • Sleep hygiene
  • Brain fog advice
  • Pacing
  • Stay involved with family, friends and activities but modified to as tolerated
  • Journal symptoms for 2 weeks
  • Follow up in 2 months
Follow-up 3 Months Later...

Functional Disability Inventory = 31 (severe; was 36)

PHQ Depression Scale 2a90 (patient) = 13 (mild-mod; was 16). No thoughts self-harm, wishing for death

Checklist Individual Strength- Mental Fatigue = 18 (moderate; was 15)

Somatic Symptom Scale (SSS8) = 22 (very high; was 17)

- Reported that she has seen "a whole lot" of improvement since her last appointment
- Feels like her symptoms are better and more manageable than they previously were

5 out 10 debilitation score (last appt 9 out of 10)

50 % baseline mood (last appt 25%)

25% baseline activity participation (last appt 0%)

75% baseline for school function (last appt 50%)
What We Did at Follow-up

- Tests: Re-ordered Vit B12, and Vit D levels
  - Ordered ferritin and Iron

- Referrals
  - Speech Therapy for cognition evaluation

- Symptom Management Recs
  - Continue pacing; avoiding push-crash cycle
  - Drink 2-3L of non-caffeinated fluid/day, salty snacks
  - Consider compression socks, particularly with marching band

- Symptom Management Recs
  - Sleep hygiene
  - Breathing exercises (John Hopkins) daily
  - Constipation management & trial peppermint oil or Heather’s Tummy Tamers for abdominal pain
  - Vaccinate against COVID-19
  - Wrote 504, including the following accommodations: use of elevator, bathroom pass, access for water and salty snacks, ability to take a break for 15 minutes as needed (in RN office if possible) for fatigue, no heavy lifting over 15 lbs
  - Plan for follow up with Long COVID Navigation Clinic in the next 2-3 months or sooner if needed
In Summary

• Similar to adults, pediatric long COVID is a complex disease with much to be learned
• Need for pediatric specific definitions, large studies with testing, trials
• Separating long COVID from pandemic effects will be difficult, but in general, many children/adolescents are struggling
• The PCH Long COVID Navigation Clinic is here to support the children and adolescents of the Intermountain West with long COVID
Questions?