# Mucosal Antiviral Cytokine Responses are Impaired in Children and Adolescents with Severe COVID-19

A Quintero, S Cohen , Z Xu, F Ye, S Mertz, K Massey, C Peachey, T Pifer, A Leber, PJ Sanchez, O Ramilo, A Mejias

Division of Infectious Disease and Center for Vaccines and Immunity, The Abigail Wexner Research Institute at Nationwide Children's Hospital

Ana.quintero2@nationwidechildrens.org
Department of Infectious Disease
700 Children's Drive, Columbus, OH 43205

## Background

- The factors associated with severe COVID-19 in pediatric patients are not fully known.
- Prior studies suggest that a robust systemic innate immune response to SARS-CoV-2 infection in children compared with adults may contribute to more favorable clinical outcomes in children with COVID-19.
- Mucosal immunity may be key to further understand the determinants of disease severity in pediatric COVID-19.

## Hypothesis

An imbalanced mucosal proinflammatory and antiviral innate immune response to SARS-CoV-2 is associated with worse clinical outcomes in children with COVID-19

## Methods

- Single-center, prospective study including children and adolescents ≤21 years of age hospitalized with symptomatic COVID-19.
- Age, sex and race matched pre-pandemic (2016-2019) healthy controls were also included.
- Nasopharyngeal samples were obtained at enrollment for measurement of SARS-CoV-2 viral loads by rt-PCR and mucosal cytokine concentrations using a 92-plex inflammation/antiviral panel (Olink).
- Severe disease was defined by the need for supplemental oxygen and/or PICU admission, and patients classified as severe *versus* non-severe based on these two parameters.
- Statistical analyses were performed in R environment and Benjamini-Hochberg applied to adjust for multiple comparisons.

## Results

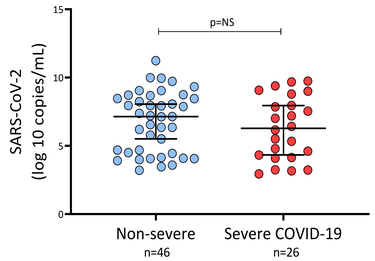
- From 3/2020 to 1/202172 we enrolled 75 children hospitalized with acute COVID-19: 28 (37%) severe and 47 (63%) non-severe

**Table 1.** Demographic and clinical characteristics

| | | Severe (n=26) | Non-Severe (n=46) | Controls (n=45) | p value |
|---|---|---|---|---|---|
| | Age (years) | 12.4 [1.2-16.3] | 1.5 [0.2-14] | 7 [0.9-15.6] | 0.13 |
| Age groups | Infants<br>1-4 yrs<br>5-11 yrs<br>12-21 yrs | 5 (19%)<br>5 (19%)<br>2 (8%)<br>14 (54%) | 23 (50%)<br>4 (9%)<br>5 (11%)<br>14 (30%) | 12 (27%)<br>7 (16%)<br>10 (22%)<br>16 (35%) | **0.04** |
| | Gender (male) | 18 (69%) | 23 (50%) | 23 (51%) | 0.24 |
| Race/Ethn. | White<br>Black<br>Asian/Multiracial<br>Hispanic | 15 (58%)<br>8 (31%)<br>1 (4%)<br>2 (8%) | 21 (46%)<br>12 (26%)<br>8 (17%)<br>5 (11%) | 21 (47%)<br>13 (29%)<br>3 (6%)<br>8 (18%) | 0.41 |
| | Underlying conditions<br>Obesity<br>Respiratory<br>Immunocompromised<br>Other | 23 (88%)<br>15 (58%)<br>6 (23%)<br>3 (11%)<br>11 (42%) | 24 (54%)<br>12 (26%)<br>2 (4%)<br>3(7%)<br>13 (28%) | N/A | **0.002** |
| | Days of symptoms | 3.5 [1.0-6.8] | 2.5 [1.0-6.8] | N/A | 0.66 |
| | Lymphopenia‡ | 17 (77%) | 16 (44%) | N/A | **0.01** |
| | CRP (mg/dl) | 3.5 [2.1-6.9] | 1.1 [0.5-3.5] | N/A | **0.004** |
| | COVID-19 targeted therapy | 17 (65%) | 1 (2%) | N/A | **<0.0001** |
| | Cardiac involvement | 6 (23%) | 2 (4%) | N/A | **0.02** |
| | Days of hospitalization | 7 [4-14.8] | 2 [1-2] | N/A | **<0.0001** |

‡Lymphopenia defined as an ALC of <4,500 cells/µl in infants, and <1,500 cells /µl in children >12 months of age

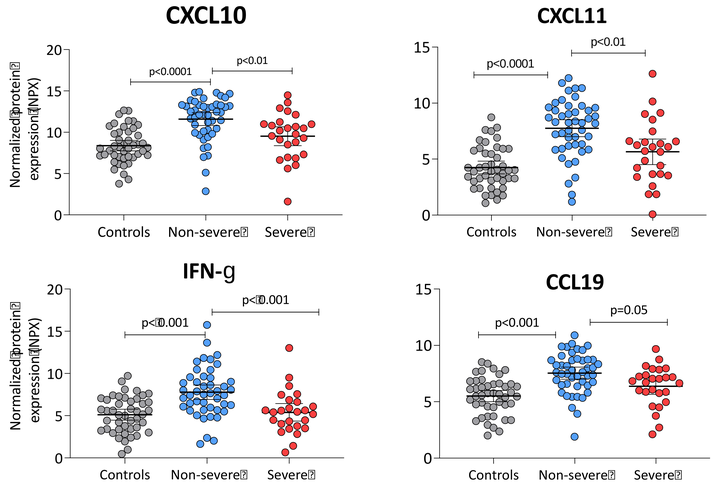
### Nasopharyngeal SARS-CoV-2 viral loads




Analysis by Mann-Whitney test

## Results

### Mucosal concentrations according to COVID-19 severity




**Nasopharyngeal cytokine concentrations in children and adolescents ≤21 years with non-severe and severe-COVID-19.** Gray represents healthy controls (n=45); blue, non-severe COVID-19 (n=46); red, severe COVID-19 (n=26). Group comparison by Kruskal Wallis and Dunn's multiple test correction.

## Summary

- Children with severe *versus* non-severe COVID-19 were older and had underlying conditions more frequently.
- SARS-CoV-2 viral loads were comparable in children with COVID-19 irrespective of disease severity.
- Children with severe COVID-19 had lower concentrations of CXCL10, CXCL11, IFN-ϒ and CCL19 compared with those with non-severe disease.

## Conclusions

These findings suggest that an impaired response of IFN-induced mucosal cytokines may contribute to SARS-CoV-2 disease severity in children.