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Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region

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Despite worldwide spread of SARS-CoV-2, few publications have reported the potential for severe disease in the pediatric population. We report 177 infected children and

young adults, including 44 hospitalized and 9 critically ill patients, with comparison of patient characteristics between infected hospitalized and non-hospitalized cohorts, as well as critically ill and non-critically ill cohorts. Children <1 year and adolescents /young adults >15 years of age were over-represented among hospitalized patients ($P = .07$). Adolescents/young adults were over-represented among the critically ill cohort. ($P = .02$).

Since the emergence and worldwide spread of Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2), published summaries have predominantly highlighted that children represent a small proportion (<2%) of COVID-19 cases, including hospitalizations and deaths.¹⁻³ Although children and young adults clearly are susceptible to SARS-CoV-2 infection, attention has focused primarily on their potential role in influencing spread and community transmission rather than the potential severity of infection in children and young adults themselves. Reanalyzed data from the epicenter of the Chinese outbreak noted that children represented 12% of infections.⁴ To date, reports of severe disease in international pediatric populations have been limited, primarily descriptive, and in the United States, limited only to incomplete public health epidemiologic data.⁵⁻⁹

Methods: This observational retrospective cohort study included 177 children and young adults with clinical symptoms and laboratory confirmed (177/1804; 9.8% of tested) SARS-CoV-2 infection treated between March 15 and April 30, 2020 at the Children's National Hospital, a large freestanding medical center located in Washington

DC. These 177 patients came to medical attention for clinical evaluation of symptoms to our emergency departments, ambulatory clinics, inpatient units, or by referral for admission from external facilities. From these 177 infected patients, we identified cohorts of non-hospitalized (N=133) and hospitalized (N=44) patients. Of the 44 hospitalized patients, we identified cohorts of non-critically ill (N=35) and critically ill (N=9) patients. The objective of the study was to determine if specific epidemiologic and clinical patient characteristics were more likely to be associated with hospitalization and/or critical care. Data were extracted from medical records and recorded in a RedCap database, including age, sex, presence or absence of underlying medical condition and presence or absence of fever or respiratory symptoms (rhinorrhea, sore throat, cough, shortness of breath), as well as other symptoms (diarrhea/vomiting, myalgia, chest pain, loss of sense of taste or smell, headache). The Fisher exact test was performed to examine differences in the distribution of categorical variables between hospitalized vs. non-hospitalized patients, as well as between hospitalized critically ill patients vs. non-critically ill patients. Continuous variables were evaluated using logistic regression. This project was submitted to the IRB and was determined to be a Quality Improvement initiative and not human subjects research.

Results:

Of the 177 pediatric and young adult SARS-CoV-2 infected patients, 44/177 patients (25%) required hospitalization, of which 35/44 (80%) were non-critically ill and 9/44 (20%) were critically ill.

Age: Children and young adults from all age groups were infected by SARS CoV-2, with a median age of 9.6 years (range 0.1-34.2 years of age). The median age of SARS-CoV-2 infected hospitalized patients compared with non-hospitalized patients was not significantly different (9.6 years versus 9.5 years), but the median age of critically ill patients compared with non-critically ill patients was significantly higher (17.3 years versus 3.6 years; $P = .04$) (**Table I**). We found no overall difference in the representation of different age groups within the hospitalized and non-hospitalized cohorts, nor between the critically ill and non-critically ill cohorts. However, we noted a bimodal distribution of patients less than one year of age and patients >15 years of age representing the largest proportion of patients within the SARS CoV-2 infected hospitalized and critically ill cohorts. Children <1 year of age and children/young adults >15 years of age each represented 32% (14/44) of all hospitalized patients, accounting for a total of 64% of hospitalizations ($p=0.07$). Adolescents and young adults > 15 years of age represented 66% (6/9) of critical care admissions ($p=0.02$). (**Figure**).

Sex: Males and females were equally represented within the total SARS CoV-2 infected cohort (52% male, 48% female), as well as the infected hospitalized cohort (50% male, 50% female). There was a predominance of males in the critically ill hospitalized cohort (67% male, 33% female); but this was not statistically significant ($p=0.26$)

Underlying Medical Conditions: Underlying medical conditions were also present in 69/177 (39%) of all patients with SARS-CoV-2 infection. The most frequent underlying diagnosis overall was asthma (35/177; 20%), but also included neurologic (6%), diabetes (3%), obesity (2%), cardiac (3%), hematologic (3%) and oncologic (1%)

underlying conditions. Underlying conditions were more common as a whole in the SARS-CoV2 infected hospitalized cohort (27/44; 63%) compared with the infected non-hospitalized cohort (42/133; 32%; $p=0.001$). Several specific underlying conditions were more common in the hospitalized as non-hospitalized patients. Specifically, neurological disorders were more common in the hospitalized cohort (8/44; 19%; $p<0.001$) compared with the non-hospitalized cohort (3/133; 2%; $p<0.001$). Additionally, cardiac ($p=0.004$), hematologic ($p=0.004$), and oncologic ($p=0.013$) diagnoses were more common in the hospitalized as compared with the non-hospitalized cohort. Although asthma was the most prevalent underlying condition overall, it was not more common in the hospitalized cohort (7/44; 16%) compared with the non-hospitalized cohort (28/133; 21%; $p=0.46$), nor more common in the critically ill cohort (2/11; 22%) compared with the non-critically ill cohort (5/35; 14%; $p=0.62$). Comparing the SARS-CoV-2 infected non-critically ill and critically ill hospitalized patients, there were no significant difference in the presence of underlying conditions overall or any specific underlying diagnosis. Of note, there was no underlying condition present in 96/177 (55%) SARS-CoV-2 infected patients overall, 16/44 (37%) hospitalized patients and 2/9 (22%) critically ill patients.

Symptoms: The majority (134/177; 76%) of SARS-CoV-2 infected patients came to medical attention with respiratory symptoms (rhinorrhea, congestion, sore throat, cough or shortness of breath) with or without fever. However, only 85/177 (48%) had both fever and respiratory symptoms present. Fever was present in 116/177 (66%) of SARS-CoV-2 infected patients but was not more common in the infected hospitalized

cohort (34/44, 77%) compared with the infected non-hospitalized cohort (82/133, 62%; $p=0.46$). Shortness of breath was more common in the hospitalized cohort (11/44, 26%) compared with non-hospitalized (16/133, 12%; $p=0.04$). However, less severe respiratory symptoms including sore throat/congestion ($p=0.004$), or cough ($p=0.003$) as well as headache ($p=0.01$) were more common in the non-hospitalized cohort. Other symptoms were also present, including diarrhea/vomiting (27/177, 15%), myalgia (25/177, 14%), chest pain (16/177, 9%) and loss of sense of smell or taste (15/177, 9%), but presence of these symptoms did not vary significantly between cohorts. Patients in the critically ill cohort were not more likely to have fever or any other specific symptom compared with the non-critically ill cohort.

Critically Ill Cohort: Eight (8) of 9 (89%) SARS-CoV-2 infected critically-ill patients required some level of respiratory support, with 4 requiring mechanical ventilation (3 meeting the definition of Acute Respiratory Distress Syndrome, 2 meeting the definition of multiple organ failure), 3 requiring Bi-level positive airway pressure (BiPAP), 1 requiring nasal non-invasive ventilation via a RAM cannula and 1 via high-flow nasal cannula. One patient had features consistent with the recently emerged Kawasaki disease-like presentation with hyper-inflammatory state, hypotension and profound myocardial depression. Details regarding these critically-ill patients including the maximum respiratory support required are summarized in the **Table 2** (available at www.jpeds.com).

Co-infection: Sixty-three (63) of the first 105 (60%) SARS-CoV-2 infected patients underwent concomitant multiplex molecular testing for respiratory pathogens; of these, 59/63 (94%) had no evidence of co-infection. 4/63 (6%) had co-detection of routine coronavirus, respiratory syncytial virus, or rhinovirus/enterovirus, of unclear clinical significance.

Discussion:

The Washington, DC metropolitan region (Maryland, Virginia, and the District of Columbia) is in the midst of a steady increase of SARS-CoV-2 circulation in the 6 weeks since March 15, 2020. In contrast to published and anecdotal reports from other countries and regions of the United States, our freestanding Children's Hospital has already evaluated and cared for a large number of children infected with SARS-CoV-2, including a significant number of children and young adults requiring hospitalization and critical care. This has occurred even prior to reaching the predicted peak surge of cases in our region at the time of this interim report. Twenty-five (25) percent of patients presenting to our hospital with symptoms required hospitalization and 5% required critical care, including need for intubation and mechanical ventilation, BiPAP and high-flow nasal cannula. No deaths have been reported to date, but critically ill patients remain hospitalized on mechanical ventilation at the time of this interim report.

Although all age groups were infected with SARS-CoV-2, the youngest (<1 year) and oldest children/young adults (15-25 years of age) were more likely to be hospitalized, and the oldest were the most likely to require critical care. Underlying conditions were

also present in 39% of patients with SARS-CoV-2 infection overall but hospitalized and critically ill patients were more likely to have underlying conditions. Conversely, approximately 55% overall, 37% of hospitalized and 22% of critically ill patients had no underlying conditions, reinforcing the concept that social distancing and hygienic measures to avoid infection should be taken seriously in the pediatric age group, as well as adults.

Although asthma was the most common underlying diagnosis present in the overall group of children and young adults with SARS-CoV-2 infection, children and young adults with asthma were not over-represented in the hospitalized cohort or in the critically ill cohort. This suggests that although children and young adults with asthma may commonly experience exacerbation in response to SARS-CoV-2 infection, asthma exacerbation is not the primary determinant of more severe disease requiring hospitalization. Many underlying diagnoses that have been associated with more severe disease in adults were also present in our pediatric and young adult patients. However, only neurologic, cardiac, hematologic, and oncologic underlying diagnoses were significantly more common in the hospitalized cohort compared with the non-hospitalized cohort, and none was more common in the critically ill compared with the non-critically-ill cohort.

With regard to symptoms, shortness of breath was more common in hospitalized compared with non-hospitalized children/young adults, but other features did not clearly distinguish them from less ill children, including presence of fever. Minor symptoms

such as congestion/rhinorrhea, sore throat, cough and headache were also present more commonly in the non-hospitalized cohort. As has been the case in adult reports, fewer than half of the patients had both fever and respiratory symptoms present at the time of their diagnosis, but the majorities have one or the other. Our critically ill cohort includes a previously well child with the newly emerged hyper-inflammatory phenotype of SARS-CoV-2-associated KD-like shock syndrome that has been identified concurrently within the same time frame at other centers internationally. The pathogenesis of this phenotype is not yet fully characterized but it is important to recognize as yet another potential severe presentation in the pediatric population.

Co-infection with other viruses was distinctly uncommon in SARS-CoV-2 infected children and young adults; 94% of those in whom this was assessed had no co-infection detected. Of the 6% who had an additional virus detected, enterovirus/rhinovirus was responsible for half, which is of unclear significance since enteroviruses are known to be shed asymptotically and detectable for months after initial infection. There was no association between viral co-detection and severity of disease.

The reasons for the observed increased severity of disease in our pediatric and young adult cohort requires additional detailed analysis, but potentially includes the comparatively higher population density in our region compared with the Western United States and/or the higher representation of African American race and/or Latino/Hispanic ethnicity in our patient population, which has recently emerged as a risk factor for more severe disease in adult populations. It recently has been noted that

introduction of SARS-CoV-2 to the Eastern United States most likely occurred as a result of importation of European strains, rather than Asian strains. Although no significant mutations conferring increased pathogenicity have yet been described, this is another potential difference that merits further analysis.

Limitations of this study include the retrospective design and the fact that transmission is still ongoing at a steady rate of increase in our region, thus this represents interim data, which will only be augmented further in the coming weeks. We plan to address the role of race and ethnicity after validation of current administrative data and have elected to defer this analysis until completed. One potential bias of this study is our regional role in providing critical care for young adults age 21-35 years of age with COVID-19. However only two such hospitalized patients were present in this study at the time of this interim report. Our study results would be expected to be generalizable to other regions on the East Coast with similar patient populations and population density, but may differ from other regions in the US that have yet to experience expansion and surge of SARS-CoV2 cases, including rural areas.

In summary, our findings highlight the potential for severe disease in this age group and inform other regions to anticipate and prepare their COVID-19 response to include a significant burden of hospitalized and critically ill children and young adults. As SARS-CoV-2 spreads within the United States, regional differences may be apparent based on virus and host factors that are yet to be identified.

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Figure Legends

Table 1: Epidemiologic Characteristics, Clinical Features and Cohort Comparison of 177 Children with Symptomatic SARS-CoV-2 Infection and Hospitalization

Figure 1: Age distribution of SARS-CoV-2 infected, hospitalized and critically ill patients

Table 2 (Online): Details of Critically Ill SARS-CoV2 Infected Children and Young Adults

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Table 1: Epidemiologic Characteristics and Clinical Features of 177 Children and Young Adults with Symptomatic SARS-CoV-2 Infection

Characteristic	Total, Non-hospitalized and Hospitalized (N=177)	Non-Hospitalized (N=133)	Hospitalized (N=44)	p value	Hospitalized, Non-Critical Care (N=35)	Hospitalized, Critical Care (N=9)	p value
Age (years)							
Median (range)	9.6 (0.1-34.2)	9.5 (0.1-34.2)	9.6 (0.1-25.6)	0.75	3.6 (0.1-21.5)	17.3 (0.1-25.6)	0.04
Distribution — no. (%)							
<1 yr	43 (24%)	29 (22%)	14 (32%)	0.22	13 (37%)	1 (11%)	0.15
1-4 yr	26 (15%)	19 (14%)	7 (16%)		6 (17%)	1 (11%)	
5-9 yr	23 (13%)	21 (16%)	2 (5%)		2 (6%)	0 (0%)	
10-14 yr	36 (21%)	29 (22%)	7 (16%)		6 (17%)	1 (11%)	
15-20 yr	37 (21%)	28 (21%)	9 (20%)		6 (17%)	3 (33%)	
>20 yr	12 (7%)	7 (5%)	5 (11%)		2 (6%)	3 (33%)	
Sex – no (%)							
Male	92 (52%)	70 (53%)	22 (50%)	0.76	16 (46%)	6 (67%)	0.26
Female	85 (48%)	63 (47%)	22 (50%)		19 (54%)	3 (33%)	
Underlying Medical Condition							
Yes	69 (39%)	42 (32%)	27 (63%)	0.001	20 (57%)	7 (78%)	0.45
No	96 (55%)	80 (60%)	16 (37%)		14 (40%)	2 (22%)	
Unknown	11 (6%)	11 (8%)	0		0	0	
Reported underlying medical condition							
Asthma	35 (20%)	28 (21%)	7 (16%)	0.46	5 (14%)	2 (22%)	0.62
Diabetes	5 (3%)	3 (2%)	2 (5%)	0.43	1 (3%)	1 (11%)	0.37
Neurologic	11 (6%)	3 (2%)	8 (19%)	<0.001	5 (14%)	3 (33%)	0.33
Obesity	4 (2%)	3 (2%)	1 (2%)	1.00	0 (0%)	1 (11%)	0.21
Cardiac	5 (3%)	1 (1%)	4 (9%)	0.004	2 (6%)	2 (22%)	0.18
Hematologic	6 (3%)	2 (2%)	4 (9%)	0.004	4 (11%)	0 (0%)	0.57
Oncologic	2 (1%)	0 (0%)	2 (5%)	0.013	2 (6%)	0 (0%)	1.00
Symptoms Present at the time of visit							
Fever	116 (66%)	82 (62%)	34 (77%)	0.06	27 (77%)	7 (78%)	0.97
Sore throat or congestion	77 (44%)	66 (50%)	11 (25%)	0.004	10 (29%)	1 (11%)	0.28
Cough	99 (56%)	83 (62%)	16 (37%)	0.003	12 (34%)	4 (44%)	0.57
Shortness of breath	27 (15%)	16 (12%)	11 (26%)	0.04	7 (20%)	4 (44%)	0.13
Diarrhea or vomiting	27 (15%)	20 (15%)	7 (15%)	0.89	5 (14%)	2 (22%)	0.56
Myalgia	25 (14%)	21 (16%)	4 (9%)	0.27	2 (6%)	2 (22%)	0.59
Chest Pain	16 (9%)	10 (8%)	6 (14%)	0.22	4 (11%)	2 (22%)	0.40
Loss of Sense of Taste and/or Smell	15 (9%)	13 (10%)	2 (5%)	0.28	2 (6%)	0 (0%)	1.00
Headache	25 (14%)	24 (18%)	1 (2%)	0.01	1 (3%)	0 (0%)	1.00

Table 2 (Online): Details of Critically Ill SARS-CoV-2 Infected Children and Young Adults

Age	Sex	Underlying Diagnosis	Clinical Features	Ventilatory Support
7 weeks	Female	Trisomy 21 Atrial Septal Defect	Symptom onset 12 days prior to admission: Tachypnea, vomiting, diarrhea. Admitted on days 3-5 of symptoms for NC 02; SARS CoV-2 PCR negative. Readmission 3 days later due to progressive tachypnea, fever. CXR with right lower lobe pneumonia. Repeat SARS Cov-2 PCR positive.	RAM cannula
4 years	Male	None	Symptom onset 5 days prior to admission: consistent with Kawasaki Disease (fever, rash, strawberry tongue, cervical lymphadenopathy) presenting in hypotensive shock. Markedly decreased myocardial function consistent with myocardial injury. Initial 2 COVID tests negative, 3 rd positive (lower respiratory specimen). Presentation consistent with severe hyper-inflammatory state (affecting myocardium) . Treated with IVIG, aspirin and anakinra.	Intubated-PRVC support Highest FiO ₂ :1.00 at intubation, but stabilized to 0.40 FiO ₂ PEEP-8
10 years	Male	Static Encephalopathy Global Developmental Delay Chronic Lung Disease Seizure disorder Asthma	Acute onset fever, increased work of breathing and decreased oxygen saturation from baseline 1-2 liter oxygen overnight requirement (no baseline daytime oxygen requirement).	BiPAP Highest FiO ₂ -0.50
16 years	Male	Microcephaly, Global Developmental Delay, Seizures, Gastrostomy	Symptom onset 3 days prior to admission: Fevers. Admitted after seizures, presented in septic shock. CXR with lobar pneumonia. Elevated troponin, acute kidney injury, liver injury, hypotensive (required pressors), hemodialysis. Treated with hydroxychloroquine.	Intubated-PRVC Highest FiO ₂ : 0.60 Highest PEEP: 10
17 years	Female	None	Symptom onset several days prior to admission: cough, congestion, myalgia. Presented with fever and dyspnea, shortness of breath. +COVID exposure	BiPAP Highest FiO ₂ : 0.35

19 years	Female	Type 1 Diabetes, Brain injury from prior DKA, Mild cognitive impairment	Symptom onset 5 days prior to admission: Fever, CXR with LLL consolidation. COVID + exposure in group home setting.	Nasal Cannula Highest O ₂ : 100% 4L/min flow
20 years	Male	Static Encephalopathy, Traumatic Brain Injury	Symptom onset 2-3 days prior to admission: Cough, dyspnea, fever. + COVID exposure (father)	BiPAP Highest FiO ₂ : 0.35
23 years	Male	None	Symptom onset 5 days prior to CNH admission: Cough, fever, progressing to shortness of breath, pleuritic chest pain, fatigue, chills, sputum production. Admitted to outside hospital 2 days prior to transfer and received hydroxychloroquine and azithromycin, tocilizumab, but progressed to intubation and transferred to Children's National on day 5 of illness. Multifocal pneumonia, MRSA bacteremia, multiorgan dysfunction, venous thrombosis, pulmonary embolism. Received second dose tocilizumab, antibiotics.	Intubated—PRVC Highest FiO ₂ : -1.00 (not weaned below 50%O ₂ since admission) Highest PEEP: 20 (while on 100% O ₂) Nitrous oxide X 6 days
25 years	Male	Morbid Obesity Asthma Hypertension Tobacco Use	Symptom onset 11 days prior to admission: Myalgias, cough. Progressive respiratory distress, hypotension leading to admission, intubation, pressor support 5 days prior to transfer to CNH. Hypotension, diarrhea, hypokalemia, elevated troponin. Treated with antibiotics, hydroxychloroquine, azithromycin, tocilizumab. Transferred to CNH on day 11 of illness. Treated with convalescent immune plasma.	Intubated-PRVC Highest FiO ₂ : 0.60 Highest PEEP: 12

Figure 1: Age Distribution of SARS-CoV-2- Infected, Hospitalized, and Critically Ill Cases

