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Pediatric Critical Care and COVID19

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Abbreviations: COVID-19: coronavirus disease 2019; PICU: pediatric intensive care unit; ICU: intensive care unit; HFNC; high flow nasal cannula; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; CRRT: continuous renal replacement therapy; ARDS: acute respiratory distress syndrome; LOS: length of stay; IQR: interquartile range; GI: gastrointestinal

Contributors Statement Page

Sebastian González-Dambrasukas and Pablo Vásquez-Hoyos designed the study, oversaw data collection and analysis, participated in drafting and editing the manuscript, and had final approval of the manuscript.

Todd Karsies designed the study, supervised data collection and analysis, carried out statistical analysis, participated in drafting and editing the manuscript, and had final approval of the manuscript.

Steven Shein designed the study, participated in data analysis and interpretation, participated in drafting and editing the manuscript, and had final approval of the manuscript.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

INTRODUCTION

COVID-19, caused by SARS-CoV2, disproportionally affects adults (children <5% in most reports)¹. Adult critical illness is characterized by acute hypoxemia, multi-organ failure, and high mortality^{2, 3}. Reported risk factors for severe illness include age, cardiorespiratory comorbidities, obesity, and laboratory findings (lymphopenia and elevated D-dimer)^{2, 4}. Pediatric reports describe low infection rates and infrequent pediatric intensive care unit (PICU) admission^{5, 6}. The largest PICU report consists of 48 North American children⁷. It describes treatments and outcomes but not with adequate granularity to understand critical pediatric COVID-19. The CAKE (Critical Coronavirus And Kids Epidemiologic) Study was designed to specifically investigate severe cases and provide detailed data. It involves over 60 centers in nearly 20 countries from the Americas and Europe. This report provides preliminary insights into our first 17 patients.

METHODS:

CAKE is a cohort study of children <19 years old with severe or critical COVID-19. The study period runs from April through December 2020. For this report, we included patients enrolled through April 23.

We defined critical COVID-19 as a positive SARS-CoV2 test and requiring ICU therapies [high flow nasal cannula (HFNC), noninvasive ventilation (NIV), invasive mechanical ventilation (IMV), vasoactive support, continuous renal replacement therapy (CRRT)]. Severe COVID-19 included those receiving mask or nasal oxygen exceeding the pediatric acute respiratory distress syndrome (ARDS) “at risk” threshold⁸.

Deidentified data were collected using a modification of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) form (<https://isaric.tghn.org/COVID-19-CRF/>). Local ethics approval was obtained with a waiver of need for consent.

RESULTS:

We enrolled 17 children from 10 PICUs in Chile, Colombia, Italy, Spain and USA. Detailed data are in the online supplement. Most were male (65%), young (median 4 years; range 0.08-18 years), and without known COVID-19 exposure (14/17). Comorbidities (Table 1; Supplemental Table 1) were common (71%) but variable. Symptoms were heterogeneous with fever and cough being most frequent (Table 1; Supplemental Table 1). Most with gastrointestinal (GI) symptoms (4/6) were also diagnosed with myocarditis (Supplemental Table 2). All these were from Europe and without prior cardiovascular disease.

Patients had frequent laboratory testing (Table 1; Supplemental Table 3). Common findings included leukocytosis, lymphopenia, plus elevated inflammatory markers, D-dimer, and troponin I. Four had viral or bacterial respiratory co-infection.

Most subjects required respiratory support (Table 2; Supplemental Table 4), with nearly half requiring IMV. Five initially treated with HFNC needed no escalation; two were intubated. One initially treated with NIV was intubated. Pulmonary-specific adjuncts were uncommon. Most patients received antibiotics; fewer received antivirals (Table 2; Supplemental Table 4). Corticosteroids, hydroxychloroquine, and tocilizumab were each prescribed to nearly half. Intravenous immune globulin (IVIG) was prescribed exclusively for myocarditis.

Pneumonia and ARDS were common diagnoses (Table 2; Supplemental Table 4). Vasoactive infusions were frequent, including three of four with myocarditis. Other organ support or complications were uncommon. Outcomes (minimum 3 weeks data) are shown in Table 4 and Supplemental Table 4. As of submission, 3 remained hospitalized, 1 in ICU, and 1 died.

DISCUSSION:

Our description exclusively about critical pediatric COVID-19 reveals an uncommon (17 patients, 60 centers) but heterogeneous disease. Children frequently had GI rather than respiratory symptoms after a brief illness and recovered quickly despite significant support. We found regional variability of diagnoses (myocarditis in Europe), treatments (remdesivir in North America), and age.

Our findings parallel recent studies describing frequent comorbidities but a short PICU stay and low mortality, contrasting with adults^{2,3,6,7}. Compared to the North American series, our study was international, younger, included only severe disease, and revealed a wider range of common symptoms⁷. We also provide critical COVID-19 laboratory findings.

We found that three children had peri-intubation arrest, markedly higher than expected⁹. At least one resulted from unfamiliar protective equipment and intubation processes. Clinicians must consider the risks before intubating these children. Pediatric COVID-19 myocarditis has not been previously reported, although adult cases are described¹⁰. It is unclear why myocarditis was only identified in Europe, but pediatric clinicians should consider cardiac involvement, particularly in those with the GI complaints common in our myocarditis patients.

This is a small case series and should be used to generate hypotheses for research rather than informing current treatment. Regional variations may limit our ability to identify outcome associations but do demonstrate regional differences. Finally, others use different definitions for COVID-19 severity, but their subjectivity could lead to patient misclassification⁶. Our definitions are simple, objective, and reflect clinically relevant distinctions.

In summary, we provide early clinical and laboratory data about critical pediatric COVID-19, which suggest a variable disease but generally good outcomes compared to adults. Targets for research include the course of organ failure in pediatric critical COVID-19, laboratory findings for predicting illness course or complications, the inflammatory response and its role in pathophysiology, best treatments, and specific organ involvement, such as myocarditis.

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Table 1: Demographics, presenting symptoms and selected laboratory findings. Results presented as n (%) unless otherwise noted

Characteristic	Result
Days of symptoms pre-admit, median (IQR)	3.5 (2, 5.8)
Days of symptoms before + test, median (IQR)	3.5 (2, 6.8)
Comorbidities ¹	
None	5 (29%)
Respiratory	1 (6%)
Cardiac	2 (12%)
Cancer/Immune	2 (12%)
Obesity	2 (12%)
Other ²	8 (47%)
Symptoms at admission ¹	
Fever	13 (76%)
Cough	9 (53%)
Dyspnea	6 (35%)
Congestion	6 (35%)
GI	6 (35%)
Other	5 (29%)
Lab Value On Admission	
Leukocytosis (WBC count > 11000 per μ L)	9 (53%)
Elevated D-dimer (> 0.5 mg/ μ L)	7 (41%)
Procalcitonin > 2 ng/mL (admission)	6 (35%)
C-Reactive Protein > 2 mg/L (admission)	13 (76%)
Lab Value Ever During Hospitalization	
Leukocytosis	12 (71%)
Lymphopenia (< 1000 per μ L)	8 (47%)
Elevated D-dimer	9 (53%)
Ferritin > 200 ng/mL	7 (41%)
Troponin I > 1 ng/mL	4 (25%)

¹Total adds up to > 100% because some had more than one comorbidity or symptom

² Includes chronic GI disorders (3), chronic neurologic disorders (2), prematurity (1), Trisomy 21 (1), and tracheomalacia (1)

Table 2: ICU Therapies and Medications. Data expressed as number (%) unless otherwise noted

Treatment		Result
Respiratory Support ¹		
	None	3 (18%)
	HFNC	7 (41%)
	NIV	4 (24%)
	IMV	8 (47%)
Vasoactive Infusion		9 (53%)
Respiratory Adjuncts ²		1 (6%)
Medications		
	Antibiotics	15 (88%)
	Remdesivir	4 (24%)
	Lopinavir/Ritonavir	1 (6%)
	Corticosteroids	9 (53%)
	Tocilizumab	7 (41%)
	Hydroxychloroquine	8 (47%)
Diagnosis/Complication		
	Pneumonia	13 (76%)
	ARDS ³	8 (47%; 2 mild, 1 moderate, 3 severe)
	Myocarditis	4 (24%)
	Cardiac Arrest	3 (18%)
	AKI	3 (18%)
Outcome		
	Died	1 (6%)
	MV Duration (days) ⁴	6 (4, 11)
	ICU LOS (days) ⁴	5.5 (4.3, 8.5)
	Hospital LOS (days) ⁴	13 (6.8, 15)

¹Percentage adds up to > 100 because some patients received > 1 modality

²Includes inhaled nitric oxide, prone positioning, and neuromuscular blockade

³Two supported with NIV so unable to classify severity

⁴Median (IQR)

Supplemental Table 1: Demographics, epidemiology, and clinical presentation

Characteristic	Patient																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Region	Europe						North America				South America						
Age (years)	13	6	0.17	14	18	4	11	0.5	17	6	0.13	0.25	0.08	3	3	5	0.8
Sex	M	M	F	M	M	F	F	M	M	M	M	F	M	F	F	M	M
Exposures																	
Known COVID +	+	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Travel	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Comorbidities																	
None	+	+	+			+							+				
Respiratory										+							
Cardiac								+									+
Renal																	
Neurologic							+									+	
Immune																	
Other				Obese	Cancer, Chemo				Immune	Obese	Premature	Airway Malacia		Congen. Liver Disease	Congen. Liver Disease	Short bowel	Trisomy 21
Presentation																	
Days of symptoms prior to admission	2	4	1	5	0 In Hosp.	4	8	2	6	2	5	7	3	7	2	3	1
Symptoms																	
Fever	+	+	+	+	+	+	+	+	+				+	+	+	+	
Cough							+	+	+	+	+	+	+	+	+		
Dyspnea					+		+		+	+		+					+
Rhinorrhea/ Congestion							+		+	+		+	+				+
Sneezing							+										
GI Symptoms	-	+	+	+		+		+	+								
Rash																	
Other	Neuro			Anuria		Abd. Pain	Neuro					Stridor, Food rejection					Food rejection

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Supplemental Table 2: Presentation and treatment details of patients diagnosed with myocarditis

Patient 2	
Presentation	Fever and vomiting, progressed to dyspnea. Electrocardiogram revealed Type I Atrioventricular block with right axis deviation prompted cardiac concern
Cardiac Imaging	Echocardiogram revealed bi-atrial dilation, severe tricuspid regurgitation, and biventricular hypokinesis with an ejection fraction of 37%
Laboratory	Troponin I 1.12 ng/mL; B-type natriuretic peptide 20518 pg/mL; viral panel negative
Treatments	Epinephrine infusion, furosemide, IVIG
Patient 3	
Presentation	Fever, vomiting, diarrhea. Severe tachycardia > 200 bpm and lab values prompted cardiac concern
Cardiac Imaging	Echocardiogram showed hypokinetic inferior-posterior wall with preserved systolic function
Laboratory	Troponin I 1.5 ng/mL; B-type natriuretic peptide 12150 pg/mL; IL-6 236 pg/mL; viral panel negative
Treatments	IVIG
Patient 4	
Presentation	Fever, vomiting, diarrhea, anuria. Organ dysfunction prompted cardiac evaluation
Cardiac Imaging	Echocardiogram showed hypokinetic left ventricle (primarily inferior-posterior) with qualitatively decreased function Cardiac MRI confirmed myocarditis
Laboratory	Troponin I 14.97 ng/mL; B-type natriuretic peptide > 35000 pg/mL; viral testing negative
Treatments	Epinephrine and milrinone infusions, NIV, furosemide, hydroxychloroquine, tocilizumab, IVIG, methylprednisolone
Complications	Atrial fibrillation requiring cardioversion, QT prolongation with hydroxychloroquine
Patient 6	
Presentation	Fever, abdominal pain, rash, conjunctivitis. Cardiac concern due to tachycardia; cardiogenic shock on day 4
Cardiac Imaging	Echocardiogram showed signs of myocarditis with hyper-echogenic papillary muscles, tricuspid and mitral valve insufficiency, and pericardial effusion
Laboratory	Troponin I 0.037; B-type natriuretic peptide 11150 pg/mL; extensive viral PCR panel from blood negative
Treatments	Dopamine, milrinone, and norepinephrine infusions; azithromycin+hydroxychloroquine, tocilizumab, methylprednisolone, lopinavir/ritonavir

Supplemental Table 3: Laboratory Findings

Result	Patient																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Hospital/ICU Presentation																	
WBC Count (cells/ μ L)	11420	12700	9400	25740	100	8900	4500	6420	10000	9100	15740	12120	16190	31400	30800	22600	8960
Lymphocytes (cells/ μ L)	1300	2200	1430	910	100	900	850	-	980	464	7500	1820	9490	8778	10472	7900	3800
Neutrophils (cells/ μ L)	9290	9700	7010	23430	0	6500	3450	-	8270	8500	5700	8860	3320	16302	19096	12100	4530
Hemoglobin (g/dL)	12.8	8.6	9.4	11.5	7.5	10.4	10.8	9.9	14.7	12.1	8.7	7.8	11.1	10	9.8	8	11.4
Platelets ($\times 10^3$)	188	341	446	312	66	76	205	209	274	473	568	466	443	403	340	602	304
aPTT (seconds)	-	-	-	-	32.7	26.8	-	-	33	-	48	-	-	-	36	32.5	32
PT (seconds)	-	12	-	-	17.2	13.6	-	-	16.2	-	-	-	-	17.1	16	17.1	17
INR	1.39	-	-	1.68	-	-	-	-	-	-	1.34	-	-	-	-	-	-
D-Dimer (μ g/mL)	1.161	6.033	1.918	4.88	0.487	2.461	0.167	-	0.93	Neg	0.51	-	-	-	-	-	-
Procalcitonin (ng/mL)	0.1	45	1.3	39	4.78	5.1	2.93	4.08	1.1	0.07	-	<0.5	<0.5	-	-	-	0.05
C-reactive protein (mg/L)	0.05	12.3	8.9	43.1	28	22.9	5.7	6.2	39.1	11.9	0.2	0.06	0.59	17.3	19.7	12.9	20.5
Ferritin (ng/mL)	-	428	136	-	2385	476	486	-	631	136	-	-	-	-	-	-	-
IL-6 (pg/mL)	-	-	236	-	-	310	-	-	-	-	-	-	-	-	-	-	-
Worst Value																	
WBC Count (high)	13400	13790	10250	35980	1960	11600	10000	7500	11700	15100	-	-	-	43300	54200	22600	8960
WBC count (low)	6030	4620	7410	15780	100	8900	3300	2700	4200	7700	-	-	-	27900	30800	12700	8960
Lymphocytes (low)	260	460	1430	1240	0	900	1220	2710	561	464	-	-	-	8778	9470	1900	3800
D-Dimer	3.761	6.033	1.918	4.88	0.467	2.461	0.587	11	6.82	Neg	-	-	-	-	-	-	-
Ferritin	-	428	136	618	2385	476	486	10712	1339	136	-	-	-	-	-	-	-
Creatine Kinase (U/L)	694	332	192	633	168	-	-	-	166	-	414	-	-	-	-	-	-
Troponin I (ng/mL)	-	1.12	1.5	14.97	37.8	0.037	-	0.21	0.074	-	0.034	-	-	-	-	-	-
Microbiology																	
SARS-CoV2 PCR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N ¹	Y	Y
Days to 1 st pos.	2	11	1	7	1	4	6	2	5	2	4	7	3	10	-	3	2
Days to 1 st neg.	n/a	n/a	n/a	13	28	n/a	n/a	n/a	18	n/a	11	n/a	n/a	n/a	n/a	n/a	n/a
Other Virus +	No	No	No	No	No	No	No	No	No	No	No	No	No	RSV	No	No	RV/EV
Bacteria +, site	MSSA, Tracheal	No	No	No	No	No	MRSA, Sputum	No	No	No	No	No	No	No	No	MSSA Line	No

¹Presumed positive due to positive COVID-19 sibling with similar symptoms

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Supplemental Table 4: Hospital treatments, diagnoses, and patient outcomes

	Patient																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Treatments																	
Respiratory																	
HFNC					+			+		+	+			+	+		+
NIV				+				+	+	+							
IMV	+						+	+	+			+	+		+	+	
ECMO																	
None		+	+			+											
ICU Treatments																	
Vasopressors	+					+	+	+	+						+	+	
Inotropes	+	+		+		+	+	+							+	+	
Nitric Oxide								+									
Proning								+		+							
NMB							+	+	+						+		
CRRT															+		
Medications																	
Antibiotics	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Antiviral (drug)	-	-	-	-	-	Lop.	Remd.	Remd.	Remd.	Remd.	-	-	-	-	-	-	-
Corticosteroids (drug)	-	-	-	+	+	+	+	+	+	+	-	-	-	+	+	-	-
Tocilizumab	+	-	-	+	+	+	+	+	+	-	-	-	-	-	-	-	-
Chloroquine/HCQ	+	-	-	+	-	+	+	-	-	+	+	+	+	-	-	-	-
Convalescent Plasma	-	No; IVIG	No; IVIG	No; IVIG	No	No; IVIG	-	-	+	-	-	-	-	-	-	-	-
Diagnoses																	
Pneumonia	+				+	+	+	+	+	+	+	+	+	+	+		+
ARDS (severity)				+			+	+	+	+		+	+		+		
				(NIV)			(Severe)	(Severe)	(Mod.)	(NIV)		(Mild)	(Mild)		(Severe)		
Neurologic	+						+									+	
Myocarditis		+	+	+		+											
Cardiac Arrest								+					+		+		
Thrombosis									+								
Myositis																	
AKI				+					+						+		
Liver Injury								+	+								
Outcomes																	
Current Status	Home	Home	Home.	Home	Ward	Home	Home	ICU	Home	Home	Home	Ward	Hone	Home	Death	Home	Home
MV Duration	4 d	n/a	n/a	n/a	n/a	n/a	11 d	20 d	8 d	n/a	n/a	6 d	4 d	n/a	3 d	3 d	n/a
ICU LOS	5 d	4 d	2 d	5 d	6 d	5 d	16 d	28 d [#]	11 d	9 d	7 d	7 d	14 d	6 d	5 d	4 d	2 d
Hospital LOS	10 d	15 d	13 d [*]	13 d	26 d [#]	13 d	28 d	28 d [#]	14 d	11 d	7 d	22 d [#]	15 d	6 d	5 d	17 d	4 d

*Prolonged for parent discharge #Still in unit Abbreviations: MP-Methylprednisolone; HC-Hydrocortisone; D-Dexamethasone; Remd.-Remdesivir; Lop.-Lopinavir/Ritonavir; HCQ-Hydroxychloroquine

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