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Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units

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IMPORTANCE The recent and ongoing coronavirus disease 2019 (COVID-19) pandemic has taken an unprecedented toll on adults critically ill with COVID-19 infection. While there is evidence that the burden of COVID-19 infection in hospitalized children is lesser than in their adult counterparts, to date, there are only limited reports describing COVID-19 in pediatric intensive care units (PICUs).

OBJECTIVE To provide an early description and characterization of COVID-19 infection in North American PICUs, focusing on mode of presentation, presence of comorbidities, severity of disease, therapeutic interventions, clinical trajectory, and early outcomes.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study included children positive for COVID-19 admitted to 46 North American PICUs between March 14 and April 3, 2020. with follow-up to April 10, 2020.

MAIN OUTCOMES AND MEASURES Prehospital characteristics, clinical trajectory, and hospital outcomes of children admitted to PICUs with confirmed COVID-19 infection.

RESULTS Of the 48 children with COVID-19 admitted to participating PICUs, 25 (52%) were male, and the median (range) age was 13 (4.2-16.6) years. Forty patients (83%) had significant preexisting comorbidities; 35 (73%) presented with respiratory symptoms and 18 (38%) required invasive ventilation. Eleven patients (23%) had failure of 2 or more organ systems. Extracorporeal membrane oxygenation was required for 1 patient (2%). Targeted therapies were used in 28 patients (61%), with hydroxychloroquine being the most commonly used agent either alone (11 patients) or in combination (10 patients). At the completion of the follow-up period, 2 patients (4%) had died and 15 (31%) were still hospitalized, with 3 still requiring ventilatory support and 1 receiving extracorporeal membrane oxygenation. The median (range) PICU and hospital lengths of stay for those who had been discharged were 5 (3-9) days and 7 (4-13) days, respectively.

CONCLUSIONS AND RELEVANCE This early report describes the burden of COVID-19 infection in North American PICUs and confirms that severe illness in children is significant but far less frequent than in adults. Prehospital comorbidities appear to be an important factor in children. These preliminary observations provide an important platform for larger and more extensive studies of children with COVID-19 infection.

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The coronavirus disease 2019 (COVID-19) pandemic, the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global health care and economic catastrophe on a scale not seen in 100 years. Human infection from the novel SARS-CoV-2 virus was first reported in Wuhan province in late November 2019. The US Centers for Disease Control and Prevention (CDC) reported the first human infection in North America on January 14, 2020.[1] To date, more than 3 million people worldwide have become infected with COVID-19, resulting in more than 215 000 deaths, with regional mortality rates ranging from less than 1% to 12%.[2]

Two initial observational studies from Wuhan province, China, reported that infants and children infrequently experience severe disease from COVID-19 compared with adults.[3,4] The first, a report of data from the Chinese Center for Disease Control and Prevention,[3] noted that only 1.3% of the 72 314 patients diagnosed with COVID-19 were younger than 20 years. In a subsequent report of 171 children younger than 16 years hospitalized in Wuhan province,[4] only 3 were admitted to the intensive care unit (ICU), and 1 of those children died. The overall disease severity in children was reported to be significantly milder than in adults. A recent CDC *Morbidity and Mortality Weekly Report*, published April 6, 2020,[5] reported that 1.7% of nearly 150 000 known cases of COVID-19 infection in the US were in children. Of the 2572 pediatric cases, 15 were admitted to an ICU, and 3 children were known to have died.

On March 14, 2020, a new voluntary International COVID-19 PICU Collaborative, comprising more than 300 pediatric ICU (PICU) and infectious disease specialists from more than 100 of the largest pediatric hospitals across 6 continents, was formalized.[6] The objective of the collaborative was to share best practices and real-time information from across the world on critical illness caused by COVID-19 in children. Since then, the group has met by virtual meeting platforms on a twice weekly or weekly basis, and at each meeting, pertinent topics are discussed and experiences shared so that all participants benefit from and contribute to the experience of others. At present, there are more than 50 North American pediatric hospitals participating and submitting data to this collaborative. The purpose of this report is to provide an early description and characterization of COVID-19 infection in North American PICUs, focusing on mode of presentation, the presence of comorbidities, therapeutic interventions, severity of disease and clinical course, and early outcomes. Of note, over the course of the 3 weeks of this sampling window, a number of PICUs in the US were repurposed, in whole or in part, to the care of critically ill adult patients with COVID-19, and while we included these sites and patients in this report, here, we focus on the experience of patients younger than 21 years.

Key Points

Question What has been the early experience of coronavirus disease 2019 (COVID-19) in pediatric intensive care units (PICUs)?

Findings In this cross-sectional study of 46 North American PICUs, between March 14 and April 3, 2020, 48 children were admitted to 14 PICUs in the US and none in Canada. A total of 40 children (83%) had preexisting underlying medical conditions, 35 (73%) presented with respiratory symptoms, and 18 (38%) required invasive ventilation, and the hospital mortality rate was 4.2%.

Meaning This early study shows that COVID-19 can result in a significant disease burden in children but confirms that severe illness is less frequent, and early hospital outcomes in children are better than in adults.

Methods

We conducted a retrospective medical record review of pediatric patients admitted to 46 participating North American PICUs with confirmed COVID-19 infection between March 14 and April 3, 2020, and with outcome follow-up through April 10, 2020. The Baylor College of Medicine served as the data coordinating center for this study and obtained institutional review board (IRB) approval with a waiver of informed consent for both local and collaborative data collection. Individual institutions contributing data obtained local IRB approval or exemption to collect and share data. All patient data were deidentified with respect to dates of birth or dates of admission and discharge or death.

Patient data included age and sex, preexisting comorbidities (ie, heart disease, developmental delay, diabetes, immune compromise, malignancy, medical complexity, obesity, posttransplant, and tracheostomy), and mode of presentation (ie, asymptomatic, respiratory, gastrointestinal, neurological, or circulatory). We describe the clinical course in terms of the presence and nature of organ failure, maximum respiratory support (ie, intubation, noninvasive ventilation, high-flow nasal cannula, oxygen therapy, or none), adjunctive respiratory support (ie, inhaled nitric oxide and prone ventilation), and additional organ support, including vasoactive medications, renal replacement therapy, plasma exchange, and extracorporeal membrane oxygenation (ECMO). We further present information regarding pharmacotherapies targeted at modulating the clinical effects of COVID-19 infection (ie, hydroxychloroquine, azithromycin, remdesivir, and tocilizumab). Clinical outcomes at the time of data closure included survival, duration of ventilation, and lengths of ICU and hospital stay for patients in whom data were complete.

We recognize the differences in practices and admission criteria across PICUs; our cohort includes acuity-adaptable special pathogen units as well as traditional PICUs. To help to incorporate this diversity into a meaningful aggregation of data, we categorized the severity of illness according to 1 of 4 categories: mild disease including fever, sore throat, cough, and/or myalgia with no dyspnea; moderate disease including fever, dyspnea, and/or chest imaging consistent with SARS-CoV-2 pneumonia and no change from baseline requirements if receiving long-term respiratory support; severe disease including fever, dyspnea, and/or chest imaging consistent with SARS-CoV-2 pneumonia, with new or increased supplemental oxygen requirement and/or ventilatory support requirement; and critical disease including respiratory failure requiring mechanical ventilation, acute respiratory distress syndrome, shock or

systemic inflammatory response syndrome, and/or multiorgan failure. Results are descriptive and presented as absolute numbers and percentages or as medians and interquartile ranges, as appropriate. Analysis was performed using Excel version 16.16.21 (Microsoft).

Results

Of the 48 children with COVID-19 admitted to participating PICUs, 25 (52%) were male, and the median (range) age was 13 (4.2-16.6) years (**Table 1**). Of the 46 hospitals in this convenience sample, 40 were located in the US and 6 in Canada. Of these, 30 pediatric hospitals had not admitted any critically ill patients with confirmed COVID-19 infection during the study period, including all of the 6 Canadian hospitals. Two US hospitals admitted children positive for COVID-19 to the PICU but were unable to obtain IRB approval within the limited time frame. The remaining 14 hospitals, all in the US, admitted a total of 58 patients to the PICU with confirmed COVID-19 infection between March 14 and April 3, 2020. The number of critically ill patients admitted to individual PICUs in this sample ranged from 1 to 17, with a median of 3 admissions per unit. The age range of patients admitted was between 26 days and 45 years. A total of 48 of 58 patients (83%) were children 21 years or younger. Ten patients were adults older than 21 years and were admitted to 3 of the participating PICUs: 2 admitted 1 adult each, and 1 admitted 8 adults. The pediatric data will be presented in this review.

Table 1. Presentation and Demographic Characteristics of 48 Children Treated in Pediatric Intensive Care Units for Coronavirus Disease 2019 (COVID-19)

Characteristic	No. (%)
Age, median (IQR), y	13 (4.2-16.6)
Age group, y	
<1	8 (17)
1-5	6 (13)
6-10	7 (15)
11-21	27 (56)
Male	25 (52)
Presentation	
Asymptomatic	1 (2)
Respiratory	35 (73)
Gastrointestinal	1 (2)
Neurological	2 (4)
Circulatory	2 (4)
Other	7 (15)
Comorbidities	
None	8 (17)
Medically complex[a]	19 (40)
Immune suppression/malignancy	11 (23)
Obesity	7 (15)
Diabetes	4 (8)
Seizures	3 (6)
Congenital heart disease	3 (6)
Sickle cell disease	2 (4)
Chronic lung disease	2 (4)
Other congenital malformations	2 (4)

Abbreviation: IQR, interquartile range.

[a] Defined as children who had a long-term dependence on technological support (including tracheostomy) associated with developmental delay and/or genetic anomalies.

Patient Characteristics and Clinical Trajectories

The diagnosis of COVID-19 infection was confirmed by polymerase chain reaction from nasal swabs. One patient (an existing in-patient) was confirmed to be positive for COVID-19 on a routine surveillance swab but remained asymptomatic from that perspective over the course of this study period. Of the remainder, most presented with respiratory symptoms, while those categorized with other presentations included 3 with diabetic ketoacidosis warranting PICU admission and a young infant with sickle cell disease and a vaso-occlusive crisis presenting primarily with bone pain. Significant comorbidities were prevalent in this pediatric cohort, with 24 patients (50%) having 1 comorbidity, 8 (17%) with 2, and 9 (19%) with 3 or more significant comorbidities. On admission, 33 (69%) were severely or critically ill, 12 (25%) required vasoactive drugs, and, while single organ failure (respiratory) affected most, 11 (23%) experienced failure of 2 or more organ systems. A total of 39 patients (81%) required respiratory support that exceeded their baseline, of whom 21 (44%) were managed noninvasively. The remaining 18 patients (38%) required endotracheal or tracheostomy ventilation. Adjunctive ventilatory interventions or extracorporeal therapies were required in 6 children (13%). Continuous renal replacement therapy was not required in the pediatric cohort.

Targeted Therapies

Clinicians targeted the viral infection with a variety of specific therapies in 28 patients (61%). The most common of these was hydroxychloroquine, either as a single agent or in combination. Azithromycin was used in 8 children as a single agent in 1 patient and in combination with hydroxychloroquine in the remaining 7 patients. Remdisivir was used in 8 patients, including as a single agent in 2 and in combination in 6. Tocilizumab was used in 5 children, including as a single agent in 1 patient, in combination with hydroxychloroquine in 1, in combination with hydroxychloroquine and azithromycin in 1, in combination with hydroxychloroquine and remdisivir in 1, and in combination with convalescent plasma in 1.

Outcomes

At the time of this report, of the 18 critically ill children requiring invasive ventilation, 2 have died, 3 still require mechanical ventilation, 7 have discontinued mechanical ventilation but remain hospitalized, and 6 have been discharged from the hospital (**Table 2**). The overall case fatality rate in this cross-sectional study was 4.2% up to the time of the report. The patients who died were aged 12 and 17 years; both had preexisting comorbidities and developed multisystem organ failure, and 1 had gram-negative sepsis prior to developing COVID-19. Fifteen children (31%) were still hospitalized, including 5 in critical condition with 1 still receiving ECMO. For those patients

Table 2. Clinical Course and Outcomes of 48 Children With Coronavirus Disease 2019 (COVID-19) Treated in Pediatric Intensive Care Units (PICUs)

Characteristic	No. (%)
Severity of illness	
Asymptomatic/mild	14 (29)
Moderate	1 (2)
Severe	16 (33)
Critical	17 (35)
Vasoactive support	12 (25)
Organ system failure	
0	6 (13)
1	30 (63)
2	7 (15)
≥3	4 (8)
Maximum respiratory support	
None	9 (19)
Oxygen only	6 (13)
HFNC	11 (23)
CPAP or BiPAP	4 (8)
Intubation/tracheostomy ventilation	18 (38)
Duration of respiratory support, median (IQR), h[a]	
Intubation	216 (138-282)
Total respiratory support	120 (40-240)
Advanced therapies	
None	41 (85)
iNO	3 (6)
ECMO	1 (2)
Plasma exchange	1 (2)
Prone ventilation	2 (4)
Pharmacotherapy	
None	20 (42)
Hydroxychloroquine	21 (44)
Azithromycin	8 (17)
Remdisivir or other antiviral therapy	8 (17)
Tocilizumab	5 (10)
2 agents	10 (21)
3 or more agents	3 (7)
Length of stay, median (IQR), d[b]	
PICU	5 (3-9)
Hospital	7 (4-13)
Outcome at follow-up[c]	
Discharged	31 (65)
Died	2 (4)
Still hospitalized	
Severe or critical condition	9 (19)
Mild or moderate condition	6 (13)

Abbreviations: BiPAP, bilevel positive airways pressure; CPAP, continuous positive airways pressure; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula oxygen therapy; iNO, inhaled nitric oxide; IQR, interquartile range.

[a] A total of 18 patients required respiratory support.

[b] PICU and hospital lengths of stay shown for 33 patients with a completed encounter by the end of follow-up.

[c] Follow-up through April 10, 2020.

with completed PICU and hospital admissions (they either died or were discharged), the median (interquartile range) PICU and hospital lengths of stay were 5 (3-9) days and 7 (4-13) days, respectively.

Discussion

In this cross-sectional study, we report the characteristics and clinical course of critically ill infants and children with COVID-19 at 46 pediatric hospitals in North America between March 14 and April 3, 2020. It is notable that only 35% of the hospitals participating in the study reported admissions of children with COVID-19 infection to the PICU, and there were no COVID-19 admissions to Canadian PICUs during the study period. Of the 48 children in this series, 18 (38%) required invasive ventilation and all but 2 survived, reflecting the markedly decreased burden of disease from COVID-19 in children compared with adults. Given the increasing prevalence of infection in the general population across North America, it is likely that an extended sampling period going forward will find a higher prevalence of hospitalization of children with COVID-19. Nonetheless, our intention here is to provide the pediatric community with an early characterization of the presentation and early clinical course of critically ill children infected with COVID-19.

Consistent with the few other initial reports on COVID-19 on children, our study found the clinical course of COVID-19 to be far less severe and the hospital outcomes to be better in critically ill children than those reported in adults. Similar to that reported in adults, in our series, comorbidities were prevalent in more than 80% of the 48 infants and children hospitalized with serious illness from COVID-19. However, in this series, we found that the most common comorbidity was medically complex, defined as children who had a long-term dependence on technological support (including tracheostomy) associated with developmental delay and/or genetic anomalies. While it is difficult to draw parallels between children and adults when considering comorbidities, children often bear the consequences of congenital conditions in contrast with adults in whom comorbidities are often acquired and may be associated with lifestyle. Obesity, which would typically be an acquired risk factor, is emerging as an important risk factor for patients with COVID-19 and has been reported in 48% of hospitalized adults.[7] In our series, obesity was notable as a comorbidity, particularly in older children, although our rates were significantly lower (20.5% of children 6 years or older had obesity).

As would be expected, most of these patients presented with respiratory symptoms, but the relative proportion presenting in this way (73%) appears to be lower than in a recently published case series in critically ill adults from the Seattle, Washington, region,[8] where acute hypoxemic respiratory failure was present in all patients admitted to the ICUs. An important subset of the patients in our series presented with only minimal or no respiratory symptoms but other important symptoms that warranted PICU admission. These included

vaso-occlusive crises in the setting of sickle cell anemia, diabetic ketoacidosis, seizures, and circulatory collapse. While there are increasing anecdotal reports of COVID-19 illness presenting with gastrointestinal tract symptoms, including abdominal pain, only 1 child in our series presented in this way. One might speculate that if gastrointestinal tract presentations are prevalent in younger patients with COVID-19 infection, then these may in fact be associated with milder clinical presentations and thus may not typically warrant PICU admission.

Of the patients requiring any respiratory support, 18 (38%) required endotracheal or tracheostomy ventilation, and 3 were still ventilated at the end of the study period. Prone ventilation, which has in some centers become almost routine in both intubated and nonintubated adults with respiratory failure, was used in 2 of the patients in this series. The PICU course was complicated by additional organ system failure in a significant minority of patients. One patient with an underlying cardiomyopathy required veno-arterial ECMO for cardiogenic shock and was still receiving ECMO (day 4 of ECMO) at the end of the study period. One patient with multisystem organ failure (renal, circulatory, and liver) received plasma exchange. No patient began renal replacement therapy.

We can be cautiously encouraged by the hospital outcomes for patients in this series, with an overall ICU mortality at the end of our follow-up period of less than 5% compared with published mortalities of 50% to 62% in adults admitted to the ICU.[8,9] However, even if we exclude the subset of patients with mild or moderate symptoms at presentation, the adjusted mortality rate (6%) remains low compared with adults.

While there are no evidence-based therapies effective against COVID-19 at this time, to our knowledge, we note that most infants and children admitted to the PICU in this series received at least 1 treatment aimed at modulating the course of the infection. Similar to the adult experience to date, hydroxychloroquine was the most frequently used agent in our series, either alone or in combination with 1 or more other agents, including azithromycin, the antiviral remdisivir, and the interleukin-6 receptor antibody tocilizumab.[10-12] It is important to note that the Infectious Disease Society of America recently recommended to restrict any proposed therapies for the treatment of COVID-19 infection to the context of formal clinical trials because of a continued lack of proven efficacy and, in some cases, increasing concerns regarding the adverse effect profiles.[13]

Finally, it is important to emphasize that the overall burden of COVID-19 infection in children remains relatively low compared with seasonal influenza. As of April 28, 2020, the CDC report 8 deaths in children 14 years or younger related to COVID-19 infection, whereas there have so far been 169 influenza-related deaths in children 14 years or younger during the 2019-2020 season, with 81 of these occurring in 2020.[14,15] Thus, up to this time of the pandemic in North America, children continue to face a far greater risk of critical illness from influenza than from COVID-19, pointing to the imperative for ongoing preventive pediatric health maintenance during this time.

Limitations

There are several limitations to our study. First, given the limited effective testing in North America for COVID-19 at the time of our study, it is possible that our findings are influenced by an ascertainment bias. That is, hospitalized severely ill children during this sampling period may not have been tested for lack of suspicion of the disease, testing capability, or both. Moreover, while 15 children were still hospitalized at the end of follow-up, a minority (less than 20%) were still severely or critically ill, and most of these patients who had been previously intubated had by then been extubated or had returned to their baseline respiratory support. Clearly, however, the limited follow-up period of 7 days for the most recently hospitalized children in this series does not exclude the possibility of worse outcomes yet to evolve in this cohort. Additionally, our presentation here of the experimental therapies provided in this series of severely ill children with COVID-19 is purely descriptive and does not imply any possible benefit from these therapies. Safe and effective treatments of COVID-19 in severely ill pediatric patients remain to be demonstrated by rigorous clinical trials.

Conclusions

The COVID-19 pandemic has had a catastrophic effect on global health. To our knowledge, this early multicenter cross-sectional study is the first of its kind from the US and adds to the emerging data of infants and children infected with COVID-19. We found the severity of illness in infants and children with COVID-19 to be far less than that documented in adults, with most PICUs across North America reporting no children admitted with this disease during the study period. Of the critically ill children with COVID-19, more than 80% had significant long-term underlying medical conditions. Overall survival and outcomes from critical illness in infants and children with COVID-19 in this series was far better than reported for adult patients. At the present time, our data indicate that children are at far greater risk of critical illness from influenza than from COVID-19. Our observations provide an important platform for further detailed studies of COVID-19 in children, with larger cohorts and longer periods of follow-up.

ARTICLE INFORMATION

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