Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

A Description of COVID-19-Directed Therapy in Children Admitted to US Intensive Care Units 2020

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Background. It is unclear how acute coronavirus disease 2019 (COVID-19)-directed therapies are used in children with life-threatening COVID-19 in US hospitals. We described characteristics of children hospitalized in the intensive care unit or step-down unit (ICU/SDU) who received COVID-19-directed therapies and the specific therapies administered.

Methods. Between March 15, 2020 and December 27, 2020, children <18 years of age in the ICU/SDU with acute COVID-19 at 48 pediatric hospitals in the United States were identified. Demographics, laboratory values, and clinical course were compared in children who did and did not receive COVID-19-directed therapies. Trends in COVID-19-directed therapies over time were evaluated.

Received 16 May 2021; editorial decision 11 November 2021; accepted 17 November 2021; published online 12 January 2022.

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Journal of the Pediatric Infectious Diseases Society 2022;11(5):191–8

https://doi.org/10.1093/jpids/piab123

Results. Of 424 children in the ICU/SDU, 235 (55%) received COVID-19-directed therapies. Children who received COVID-19-directed therapies were older than those who did not receive COVID-19-directed therapies (13.3 [5.6-16.2] vs 9.8 [0.65-15.9] years), more had underlying medical conditions (188 [80%] vs 104 [55%]; difference = 25% [95% CI: 16% to 34%]), more received respiratory support (206 [88%] vs 71 [38%]; difference = 50% [95% CI: 34% to 56%]), and more died (8 [3.4%] vs 0). Of the 235 children receiving COVID-19-directed therapies, 172 (73%) received systemic steroids and 150 (64%) received remdesivir, with rising remdesivir use over the study period (14% in March/April to 57% November/December).

Conclusion. Despite the lack of pediatric data evaluating treatments for COVID-19 in critically ill children, more than half of children requiring intensive or high acuity care received COVID-19-directed therapies.

Key words: COVID-19; intensive care unit; pediatric; remdesivir; treatment.

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and subsequent coronavirus disease 2019 (COVID-19) pandemic necessitated rapid identification of effective acute COVID-19-directed therapies. Although the majority of disease occurs in adults, children account for approximately 11% of all US COVID-19 reported cases [1]. While pediatric disease is generally mild, severe acute COVID-19 can occur in children. From March 1, 2021 to July 25, 2021, the cumulative COVID-19 associated hospitalization rate in children was 8.0/100 000, but approximately one-third of children hospitalized with COVID-19 require management in an intensive care unit (ICU) [2]. Despite the occurrence of severe pediatric disease, few clinical treatment trials have included children [3], and the majority of treatment guidelines are geared toward adults [4, 5]. Pediatric-specific recommendations regarding which patients should receive treatment and which therapeutics should be used rely on expert opinion based on data extrapolated from adult studies [6, 7].

Recommended therapies have focused on drugs with either proposed antiviral and/or immunomodulatory activity [4, 8], and treatment patterns and recommendations in adults have evolved during the pandemic as new evidence has become available [9]. Although data on children are lacking, children were included in the emergency use authorizations (EUA) of some agents, including hydroxychloroquine and remdesivir [10, 11]. Anecdotal experience suggests that many potential therapies, the majority of which are off-label, are being used in children hospitalized with COVID-19 and that their use is rising; however, a comprehensive assessment across multiple US hospitals has not been performed. Therefore, our study sought to describe the characteristics of US children admitted to the ICU/step-down unit (SDU) for COVID-19 who received COVID-19-directed therapies and the patterns of use in children across US pediatric hospitals during 2020.

METHODS

Study Design

For this case series, active surveillance was performed in the Overcoming COVID-19 network at 48 US sites to identify persons aged <21 years hospitalized with COVID-19-related complications [12, 13]. Cases were identified by site investigators and their research team, who abstracted data from the medical record into a standardized case report form. Study data, including patient demographics, underlying medical conditions, signs and symptoms, clinical course, laboratory values, diagnostic imaging, pharmacologic and non-pharmacologic therapeutics, and outcomes, were entered into a secure, web-based software platform, Research Electronic Data Capture (REDCap, Vanderbilt University) [14]. The study was approved by the central institutional review board (IRB) at Boston Children's Hospital and each site's IRB. The study was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy, which included a waiver of consent.

Participants

Case patients from the registry were included if they were aged <18 years and hospitalized in the ICU or SDU at any time from March 15, 2020 to December 27, 2020 due to acute symptomatic COVID-19 based on a positive result from a real-time reverse transcription–polymerase chain reaction (RT-PCR) test. We excluded case patients with a diagnosis of multisystem inflammatory syndrome in children (MIS-C), as defined by CDC criteria [15], and those who were admitted to the ICU/SDU but had asymptomatic SARS-CoV-2 infection (eg, testing obtained solely for preoperative and/or admission screening).

Treatments

The following treatments were considered COVID-19-directed therapies (COV-19Tx): remdesivir, convalescent plasma, hydroxychloroquine, protease inhibitors (lopinavir/ritonavir), azithromycin in combination with other COV-19Tx, and immunomodulatory therapies (ie, interferon α, interferon β1, tocilizumab, siltuximab, anakinra, systemic steroids, tumor necrosis factor α inhibitors, emapalumab, and Janus kinase inhibitors).

Patient Demographic and Clinical Characteristics

Patients were defined as "previously healthy" if they had no underlying medical conditions as previously defined [12] (excluding obesity) and were not receiving prescription

medications for chronic conditions. Obesity was defined either through clinician-diagnosed reporting or national reference standards for body mass index (BMI [kg/m^2]) for patients aged ≥2 years [16]. To describe the clinical characteristics and disease severity of patients, we evaluated 3 features: (1) previously described laboratory indicators of inflammation in hospitalized COVID-19 subjects (platelet count, neutrophil-to-lymphocyte ratio [NLR], and C-reactive protein [CRP]) with non-missing values for at least 70% of patients [12, 13]; (2) diagnosis of pediatric acute respiratory distress syndrome (PARDS) defined as meeting the following criteria within the same 24-hour period: acute onset of hypoxemia, chest imaging with new infiltrates, respiratory failure not explained by cardiac failure or volume overload, PaO_2/FiO_2 ratio ≤300 or SpO_2/FiO_2 ≤264 (if SpO_2 ≤97), on continuous positive airway pressure (CPAP) ≥5 cm H_2O or bilevel positive airway pressure (BiPAP) or invasive mechanical ventilation [17]; and (3) need for certain clinical interventions (eg, respiratory support, vasoactive medications).

Statistical Analysis

We determined demographic characteristics, laboratory values, and hospital course of patients receiving ≥1 COV-19Tx vs no COV-19Tx. Continuous variables were expressed as medians with interquartile ranges (IQR), and categorical variables were expressed as counts and percentages. For univariate comparisons between the COV-19Tx and no COV-19Tx groups, a Kruskal-Wallis test was used for continuous variables. Proportions of treatments by month were compared using chi-squared statistics. Significance threshold was $P < .05$. Risk differences for categorical variables were calculated using the risk difference command in R from the fmsb package [18, 19]. We did not impute missing data. All analyses were conducted in R 4.0.2 (R Project for Statistical Computing).

Table 1. Patient Characteristics of Children With COVID-19, by Treatment With COVID-19-Directed Therapies (COV-19Tx)[a]

	COV-19Tx (n = 235, 55.4%)	No COV-19Tx (n = 189, 44.6%)	Risk Difference (95% CI) or *P*-value
Male	143 (60.9%)	100 (52.9%)	7.9% (−1.5% to 17.4%)
Age (years), median (IQR)[b]	13.3 (5.6, 16.2)	9.81 (0.7, 15.9)	<.001
Age category (years)			
<1	22 (9.4%)	54 (28.6%)	−19.2% (−26.6% to −11.8%)
1-5	38 (16.2%)	24 (12.7%)	3.5% (−3.2% to 10.2%)
6-12	56 (23.8%)	40 (21.2%)	2.7% (−5.3% to 10.6%)
13-17[b]	119 (50.6%)	71 (37.6%)	13.1% (3.7% to 22.5%)
Race/ethnicity			
White, non-Hispanic	53 (22.6%)	45 (23.8%)	−1.3% (−9.3% to 6.8%)
Black, non-Hispanic	69 (29.4%)	52 (27.5%)	1.8% (−6.8% to 10.5%)
Hispanic or Latino	90 (38.3%)	69 (36.5%)	1.8% (−7.5% to 11.0%)
Other, non-Hispanic	17 (7.2%)	12 (6.3%)	0.9% (−3.9% to 5.7%)
Unknown	8 (3.4%)	15 (7.9%)	−4.5% (−9.0% to 0.0%)
Insurance status			
Public insurance[b]	177 (75.3%)	122 (64.6%)	10.8% (2.0% to 19.5%)
Private insurance	42 (17.9%)	50 (26.5%)	−8.6% (−16.6% to −0.6%)
Other or unknown	16 (6.8%)	17 (9.0%)	−2.2% (−7.4% to 3.0%)
Underlying conditions			
At least one underlying condition[b]	188 (80.0%)	104 (55.0%)	25.0% (16.2% to 33.7%)
Respiratory[b]	98 (41.7%)	45 (23.8%)	17.9% (9.1% to 26.6%)
Cardiovascular[b]	36 (15.3%)	16 (8.5%)	6.9% (0.8% to 12.9%)
Neurological/neuromuscular[b]	72 (30.6%)	25 (13.2%)	17.4% (9.8% to 25.0%)
Oncologic, immunosuppressive, or rheumatologic/autoimmune[b]	44 (18.7%)	10 (5.3%)	13.4% (7.5% to 19.4%)
Hematologic	19 (8.1%)	19 (10.1%)	−2.0% (−7.5% to 3.6%)
Renal or urologic	25 (10.6%)	11 (5.8%)	4.8% (−0.3% to 10.0%)
Gastrointestinal/hepatic[b]	66 (28.1%)	27 (14.3%)	13.8% (6.2% to 21.4%)
Endocrine	41 (17.4%)	30 (15.9%)	1.6% (−5.5% to 8.7%)
Genetic/metabolic (excluding obesity)	28 (11.9%)	13 (6.9%)	5.0% (−0.5% to 10.5%)
Obesity[b]	68/201 (33.8%)	20/127 (15.7%)	18.1% (9.0% to 27.2%)

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

[a]COVID-19-directed therapies (COV-19Tx): remdesivir, convalescent plasma, hydroxychloroquine, protease inhibitors (lopinavir/ritonavir), azithromycin in combination with other COV-19Tx, and immunomodulatory therapies (ie, interferon α, interferon β1, tocilizumab, siltuximab, anakinra, systemic steroids, tumor necrosis factor α inhibitors, emapalumab, and Janus kinase inhibitors).

[b]Variables where the 95% confidence interval for difference in proportions did not include the null value or was significant at $P < .05$.

RESULTS

From March 15, 2020 to December 27, 2020, of the 1958 individuals in the registry, 424 (21.7%) patients hospitalized with acute COVID-19 in the ICU/SDU from 48 hospitals in 29 states met our inclusion criteria (Supplementary Figure 1). The characteristics of the 235 (55.4%) children receiving at least one COV-19Tx compared to the 189 not receiving COV-19Tx are summarized in Table 1. Children who received COV-19Tx were older than those who did not receive COV-19Tx (median 13.3 vs 9.8 years; $P < .001$). Black non-Hispanic and Hispanic or Latino children made up 28.5% and 38.7% of children admitted to the ICU/SDU with COVID-19, respectively, but no significant difference in receipt of COVID-19Tx based on race and ethnicity was noted. Treated children also had a higher frequency of underlying medical conditions (188 [80%] vs 104 [55%]; difference = 25% [95% CI: 16% to 34%]) and obesity (68 of 201 [33.8%] vs 20 of 127 [15.7%]; difference = 18% [95% CI: 9% to 27%]). Forty-four of 54 (81.5%) children with rheumatologic/autoimmune, immunosuppressive, and/or oncologic conditions received COV-19Tx, comprising the underlying medical conditions with the highest proportion of treated children. As shown in Figure 1, the patients receiving COV-19Tx were more severely ill compared with those who did not receive COV-19Tx by multiple criteria (all *P*-values <.001). Additionally, a higher proportion of treated patients had NLR >5, CRP >3 mg/dL, and platelet counts <150 000 cells/μL. Treated patients also more frequently received respiratory support (206 [88%] vs 71 [38%]; difference = 50% [95% CI: 34% to 56%]) and more often met PARDS criteria. The COV-19Tx group had a longer median length of ICU stay of 6 days (IQR: 3-12.25 days) compared with 2 days (IQR: 1-4 days) [$P < .001$] in the non-COV-19Tx group, as well as a longer length of hospital stay at 10 days (IQR: 5-17 days) vs 3 days (IQR: 2-7 days) [$P < .001$]. Subject participation in COV-19 Tx clinical trials was uncommon (n = 32, 7.5%).

Acute COVID-19 Therapies

Of the 235 patients who received COV-19Tx, 141 (60%) received ≥2 COV-19Tx (Supplementary Table 1). The most commonly administered COV-19Tx regimens were remdesivir and systemic steroids (26.8%); systemic steroids only (23.0%); remdesivir only (11.9%); and remdesivir, azithromycin, and systemic steroids (8.1%) (Supplementary Table 1). Overall, remdesivir was the most commonly administered antiviral agent (150 of 235 [61.3%]); it was administered as the sole therapeutic in 28 children and with other therapies in 122 children. The median length of remdesivir treatment was 5 days (IQR: 5-5 days). Systemic steroids were the most commonly administered immunomodulatory agent (172 of 235 [73.2%]), with steroid monotherapy administered to 53 children and used with additional therapies in 119 children (Supplementary Table 1). Of the 172 children receiving steroids, 70%, 28%, and 18% received dexamethasone, methylprednisolone, and hydrocortisone, respectively. The majority of patients (28/31, 90.3% received hydrocortisone at standard (ie, non-stress) doses. Other administered therapies included convalescent plasma (29 of 235 [12.3%]) and hydroxychloroquine (27 of 235 [11.5%]). The median

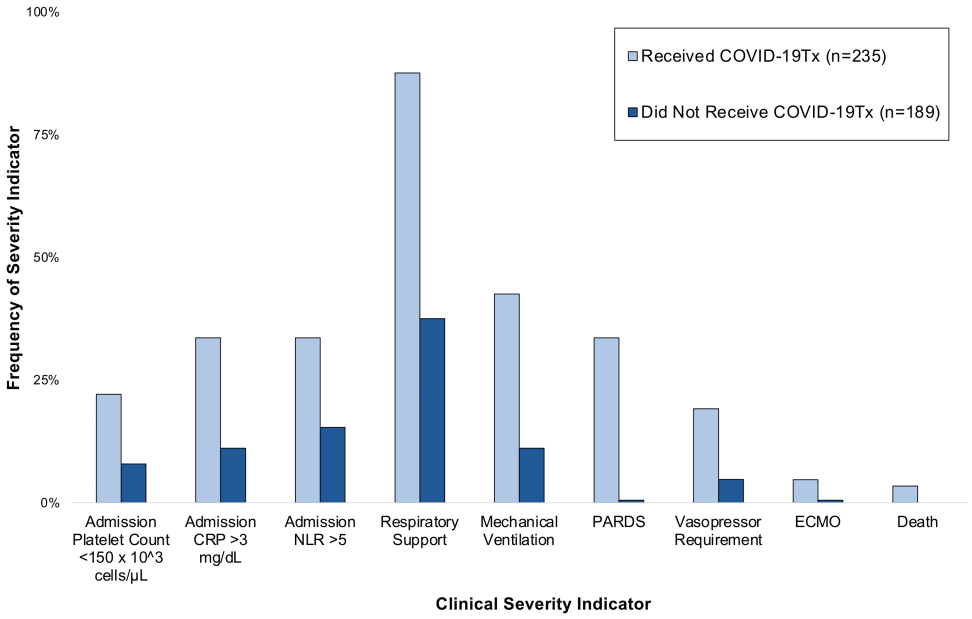

Figure 1. Acute COVID-19 patients by clinical severity*, grouped by receipt of COVID-19-directed therapies (COV-19Tx) during hospitalization. **P* values for all clinical severity indicators were <0.001. Abbreviations: COV-19Tx, COVID-19 Treatments; CRP, C-reactive protein; NLR, Neutrophil-to-lymphocyte ratio; PARDS, pediatric acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.

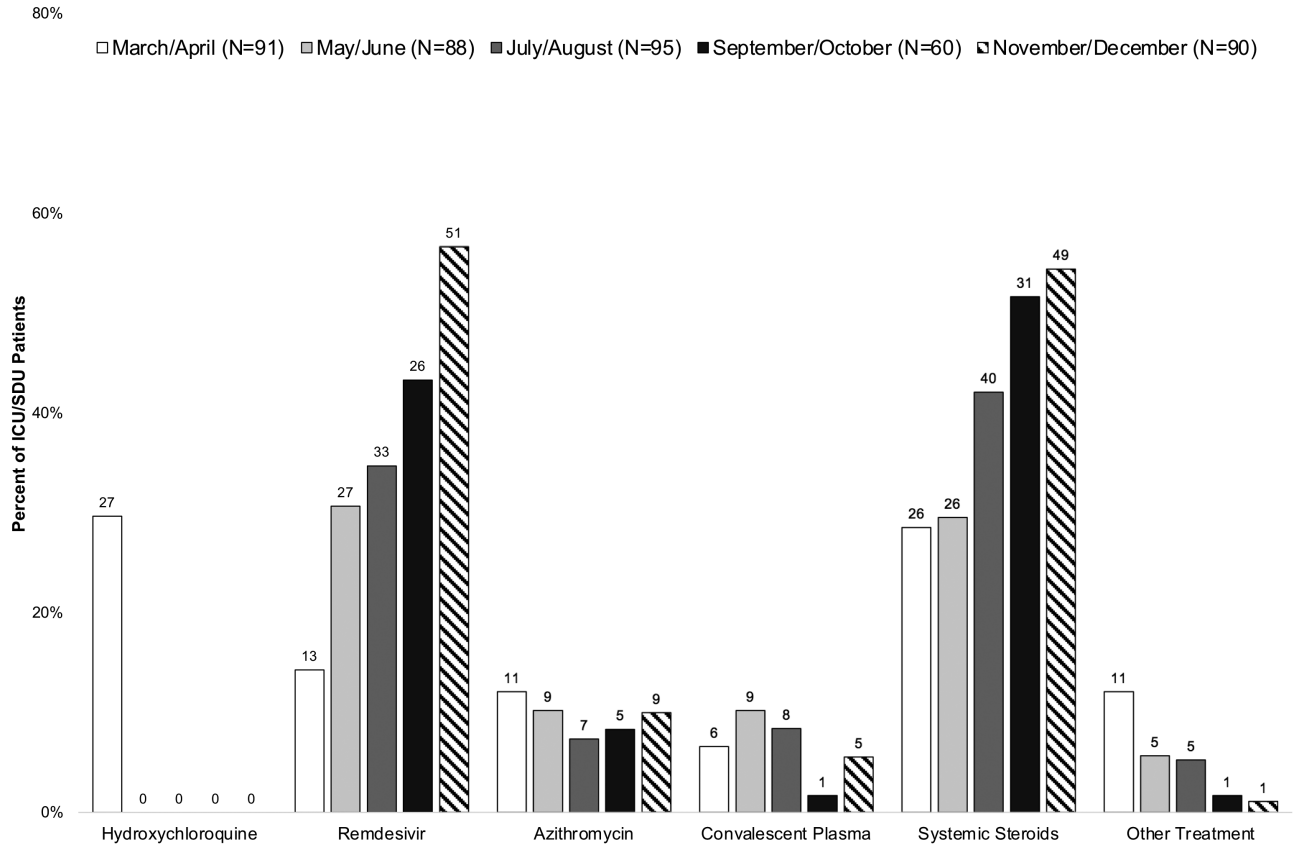

Figure 2. Variability of COVID-19-directed therapies (COV-19Tx) in children and adolescents admitted to the intensive care or step-down unit for acute COVID-19 by month of hospital admission*. *Significant difference (P <0.001) in reduction in treatment use of hydroxychloroquine and increase in remdesivir use from March/April to November/December. Other treatments included protease inhibitors (lopinavir/ritonavir), non-steroid immunomodulatory therapies (interferon α, interferon β1, tocilizumab, siltuximab, anakinra, tumor necrosis factor α inhibitors, emapalumab, and Janus kinase inhibitors).

length of hydroxychloroquine treatment was 5 days (IQR: 4-5 days). Hydroxychloroquine use was common in March/April but decreased starting in May/June (P < .001), whereas remdesivir administration increased (P < .001) over the study period (Figure 2). Remdesivir was used in the majority of patients across all age groups (Supplementary Table 2). The overall frequency of hydroxychloroquine use was low, but the proportion was similar across all age groups with the exception of children aged 1-5 years (13%-14% vs 3%) (Supplementary Table 2).

DISCUSSION

This case series included 424 severely ill children admitted with acute COVID-19 to the intensive care or high acuity units from March 15, 2020 through December 27, 2020 across 48 US hospitals, and 55% of the patients received at least one COVID-19-directed therapy. In treated patients, most received more than one COVID-19-directed therapy despite lack of evidence supporting efficacy in children and lack of access to available clinical trials assessing benefit. Older children, obese children, and those with underlying medical conditions were more likely to receive COVID-19-directed therapies. Although all children in our cohort were admitted to the higher acuity units, children who received COVID-19-directed therapies more frequently had life-threatening COVID-19 complications requiring respiratory and/or vasopressor support with more meeting the PARDS criteria [17]. Adult and pediatric guidelines recommend COVID-19-directed therapies for patients requiring these life-support interventions [6, 7]. But current adult patient guidelines also recommend the use of COVID-19-directed therapies for patients requiring supplemental oxygen [4, 5]. Use of COVID-19-directed therapies in children with severe respiratory disease receiving oxygen support that did not require other life support was less common.

Our findings differ from those reported by the COVID-Net. COVID-Net surveillance investigators evaluated data from 99 counties in 14 states from March 2020 to June 2020 reporting that 7.8% (16/206) of children received a COVID-19-directed therapy [9]. Their evaluation included all hospitalized children early in the pandemic, likely explaining the lower frequency of use compared to our cohort admitted to the ICU or SDU. In one study of 48 children admitted to North

American pediatric ICUs from March 14, 2020 to April 3, 2020, 61% of the children received COVID-19-directed therapies, and similar to our cohort most of these patients also had a documented underlying medical condition [20]. In both of the early pandemic study reports, hydroxychloroquine was the most commonly used COVID-19-directed therapy, similar to our case patients in March/April. This trend was also documented in European children early in the pandemic [8]. Decreasing use of hydroxychloroquine coincided with the US Food and Drug Administration (FDA) revocation of EUA for hydroxychloroquine on June 15, 2020 [21].

We report a steep increase in the use of remdesivir over 2020, with almost 60% of children hospitalized with severe COVID-19 receiving it during November-December. The increased use over time corresponds with published guidance from the FDA, which issued an EUA for remdesivir for severe disease on May 1, 2020, updated the EUA to no longer limit use to severe disease on August 28, 2020, and ultimately approved the drug on October 22, 2020 for patients ≥12 years of age and weighing ≥40 kg [22]. In a prior study, we noted that remdesivir was the most common antiviral drug administered for severe acute COVID-19, with many of these children also receiving steroids; however, the current study adds information about temporality and characteristics of patients receiving COVID-19-directed therapies [13].

The patterns in therapeutic use observed in our cohort are consistent with typical approaches to pediatric drug therapy, in which off-label use of products in adults is extended to pediatric populations over time [23]. Early in the pandemic, Single-Patient Expanded Access (compassionate use) requests were the only available method to access the drug for children, leading to potential delays in use of remdesivir in children. In the context of a pandemic due to an emerging pathogen, robust evidence for use of therapeutics in children, as well as adults, is likely to be lacking, especially early on. In particular, limited pharmacokinetic and safety data were available for pediatrics early in the pandemic, despite its use in the pediatric population. Few children in our study were enrolled in a clinical trial, highlighting the importance of rapidly planning and implementing pediatric clinical trials to keep pace with clinical knowledge in adult populations. Inclusion of adolescents in adult trials is increasingly supported and the FDA has issued guidance encouraging sponsors to consider enrollment of multiple pediatric age groups in parallel—as opposed to a step-wise extension to younger age groups—when safety concerns do not warrant age-specific approaches [24, 25]. Pharmaceutical companies and the FDA should leverage existing pediatric networks with the infrastructure to perform clinical trials in order to expedite pediatric drug studies.

In our cohort, other adjunctive COVID-19-directed therapies, including steroids, convalescent plasma, tocilizumab, and anakinra, were also administered, with steroids being the most common drug class used. Although pediatric experts suggested that these immunomodulatory agents be administered within the context of a clinical trial, few trials have enrolled children [26]. Without direct evidence in children, clinicians extrapolate from adult data for guidance. Given the variability in drug responses and dosing between young children and adults, this may lead to inaccuracies. Lastly, numerous COVID-19-directed therapy combinations were prescribed in our cohort, with some patients receiving 4- to 5-drug combinations with little pediatric data available regarding the safety of COVID-19-directed therapy combinations.

This study provides a broad evaluation of the use of and trends in COVID-19-directed therapies during the first 10 months of the COVID-19 pandemic. Currently published pediatric data highlight the use of hydroxychloroquine early in the pandemic. Our data demonstrate the changing treatment patterns over time, which mirrored evolving national recommendations based on adult data and targeted toward adult patients [4, 9]. Furthermore, peaks in SARS-CoV-2 infections have occurred at varying times in different geographic locations. Regions with surges early in the pandemic likely had different COVID-19-directed therapy prescribing patterns than regions that experienced surges later in the pandemic because adult COVID-19-directed therapy recommendations evolved over time. Thus, a strength of this multi-center, geographically diverse surveillance system is the ability to provide national data to examine treatment trends for severe pediatric COVID-19 during the pandemic.

In this observational study, we did not attempt to evaluate the effectiveness of COVID-19 treatments using regression modeling because of confounding by severity [27], as the majority of patients with the highest severity received treatment (eg., 88% of treated patients had received COVID-19 treatments vs 38% of untreated patients). Furthermore, we were unable to apply analytic methods with accuracy to evaluate the effectiveness of anti-COVID-19 treatments in this report due to the heterogeneity in treatments by site and calendar time and the small sample sizes. Even with homogeneity in treatments and restriction of our cases to ICU patients, the magnitude of confounding by severity in our dataset would essentially translate to comparison of severe treated cases with milder untreated cases. This might result in biased findings of null effect or possible association between treatment and adverse outcomes where none exists.

Our study highlights that children most severely ill children with COVID-19 are receiving COVID-19 therapies. Evaluating their effectiveness in this population is a top priority. Ideally, such evaluation would be done through blinded randomized placebo-controlled trials. Unfortunately, randomized trials excluded most children early in the COVID-19 pandemic. Sometimes observational data collected through networks such as Overcoming COVID-19 can offer opportunities to evaluate the effectiveness of treatments under real-world settings. This

was recently done by our group for treatment of MIS-C, where glucocorticoids plus intravenous immune globulin (IVIG) was associated with reduced risk of new or persistent cardiovascular dysfunction as compared with IVIG alone [28]. In that analysis, we applied propensity score matching to balance treatment groups and mimic intention to treat analysis of a randomized trial. Such analyses can control for confounding factors that might influence treatment choices [29]. However, for MIS-C, treatments were much more homogenous, sample sizes were larger, and we had patients of equal severity treated with IVIG vs IVIG plus glucocorticoids. In contrast, this was not the situation with COVID-19 treatments in our dataset. Consequently, we were unable to make valid inferences on the effects of these treatment data under these observational circumstances.

This study has a number of additional limitations. First, although a geographically diverse network of sites participated, this does not represent all children hospitalized with acute COVID-19 in the United States. Second, reasons for treating or not treating with COVID-19-directed therapies were not collected. The choice to use (or not use) COVID-19-directed therapies could have been related to a variety of reasons, including limited drug availability, lack of safety and/or efficacy data, or provider preference. Third, clinical experience due to geographic variation in COVID-19 incidence and variability over time in availability of some COVID-19-directed therapies (eg, remdesivir) may have affected the treatments administered, but collecting data on drug availability at participating sites was beyond the scope of our study. Finally, these data preceded circulation of the Delta variant, and prescribing practices may have changed.

In a large sample of critically ill US children with acute COVID-19, the majority received COVID-19-directed therapies, most often remdesivir and/or steroids. As the pandemic evolved, over half of the patients received more than one COVID-19-directed therapy. Notably, these drugs are being prescribed off-label and with no primary data in children. Having organized, sponsored pediatric networks in place, especially in the midst of a pandemic, can facilitate the inclusion of children in prospective clinical studies to generate timely, high-quality evidence to guide their treatment [3].

Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. This work was supported by the United States Centers for Disease Control and Prevention, the National Institutes of Health NIDDK K23119463 (Fitzgerald) and NHLBI K23HL150244 (Rowan), and the Burroughs Welcome Fund Innovation in Regulatory Science Award (Bourgeois)

Potential conflicts of interest. All authors: Dr. Schuster reports receiving money from Merck for a research study for RSV outside of the submitted work. Dr. Nakamura was involved in the Gilead-sponsored pediatric remdesivir trial at Boston Children's Hospital. Dr. Bourgeois receives support from the Harvard-MIT Center for Regulatory Science. Dr. Hobbs reports receiving consultancy fees from BioFire (Biomerieux). No other disclosures were reported. No reported conflicts. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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