Corticosteroids and Other Treatments Administered to Children Tested for SARS-CoV-2 Infection in Emergency Departments

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ABSTRACT

OBJECTIVE: We sought to determine if corticosteroid administration is associated with a SARS-CoV-2 nucleic acid test-positive result and to describe therapies administered to SARS-CoV-2 infected children.

METHODS: We collected cross-sectional data from participants recruited in 41 pediatric emergency departments (ED) in 10 countries between March 2020 and June 2021. Participants were <18 years old, had signs or symptoms of, or risk factors for acute SARS-CoV-2 infection, and had nucleic acid testing performed. To determine if SARS-CoV-2 test status was independently associated with corticosteroid administration, we used a multivariable conditional logistic regression model matched by study site to compare treatments administered based on SARS-CoV-2 test and disposition status. This analysis was repeated for the subgroup of study participants who were hospitalized.

RESULTS: 30.3% (3,121/10,315) of participants were SARS-CoV-2-positive. Although remdesivir was more commonly administered to SARS-CoV-2-positive children, use was infrequent (25/3120 [0.8%] vs 1/7188 [0.01%]; $P = .001$). Corticosteroid use was less common among SARS-CoV-2-positive children (219/3120 [7.0%] vs 759/7190 [10.6%]; $P < .001$). Among hospitalized children, there were no differences in provision of inotropes, respiratory support, chest drainage or extracorporeal membrane oxygenation between groups. Corticosteroid administration was associated with age, history of asthma, wheezing, study month, hospitalization and intensive care unit admission; it was not associated with a positive SARS-CoV-2 test result overall (aOR: 0.91; 95%CI: 0.74,

1.12) or among the subgroup of those hospitalized (aOR: 1.04; 95%CI: 0.75, 1.44).

CONCLUSIONS: Few disease-specific treatments are provided to SARS-CoV-2-positive children; clinical trials evaluating therapies in children are urgently needed.

WHAT'S NEW

Few SARS-CoV-2 infected children receive SARS-CoV-2 specific therapies. There was no independent association between corticosteroid use and SARS-CoV-2 test status, even among those hospitalized. There is a need for clinical trials that provide pediatric-specific data to guide therapy in children.

OVER THE COURSE of the SARS-CoV-2 pandemic, the pediatric burden of disease has increased. As of December 2021, children represented 15.7% of all cases reported in the United States,[1] and the hospitalization rate among children during the fourth wave exceeds those seen during earlier waves[2] with more than 30% of hospitalized children having severe COVID-19.[3] However, we have limited knowledge of treatments provided to children with COVID-19 in emergency departments (ED) and during hospitalization and such data can identify interventions in need of pediatric-specific evidence to inform use.

Reports from early 2020 that included 115 hospitalized children described the use of hydroxychloroquine (30% −37%), remdesivir (6%−8%), corticosteroids (4% −11%), and tocilizumab (2%−5%).[4,5] In one study, additional treatments included anticoagulation (28%), azithromycin (20%), and anakinra (11%).[4] A recent multinational database study reported significant heterogeneity across countries in the use of treatments among hospitalized children.[6] Notably, corticosteroids were administered to between 25% and 35% of children in the US but just 7% of children in Korea. Moreover, a study from the United Kingdom reported that 69% of children hospitalized with COVID-19 received antibiotics.[7]

Although several drugs have recently been approved for use in children with COVID-19 (eg, monoclonal antibodies), the extension of their use to include neonates and young children was based primarily on adolescent and adult safety and efficacy data.[8] Moreover, the mainstay of therapy among critically ill adults, dexamethasone,[9] remains essentially an unevaluated option in children and although pediatric data are lacking, a clinicaltrials.gov search on December 17, 2021 revealed no active COVID-19 corticosteroid pediatric studies. Thus, there are few pediatric SARS-CoV-2 specific treatment options available based on pediatric clinical trial data.[10]

To shed light on this issue, we sought to describe and compare treatments provided to children tested for SARS-CoV-2 infection based on test result and disposition status. Treatments provided were grouped based on timing of administration: 1) prior to the ED visit (ie, prehospital), and 2) during the hospital visit (ie, in the ED or the subsequent hospitalization (if required)). We additionally determined if, among hospitalized children, SARS-CoV-2 test-result status was associated with corticosteroid administration. As most children with COVID-19 discharged home from the ED are unlikely to experience complications, we hypothesized that among these children, treatments would not differ by SARS-CoV-2 test status. Among those hospitalized, given the benefits seen in adults associated with corticosteroid administration, we hypothesized that a higher proportion of SARS-CoV-2-positive children would receive corticosteroids.

METHODS

STUDY DESIGN & SETTING

The Pediatric Emergency Research Network's (PERN)-COVID-19 prospective study recruited children with suspected acute SARS-CoV-2 infections presenting for care in one of 41 participating pediatric EDs in 10 countries between March 18, 2020 and June 15, 2021.[11] We report cross-sectional data (database export performed July 26, 2021) related to the index ED visit and subsequent hospitalization, if required.

PARTICIPANTS & RECRUITMENT

Eligible participants were <18 years old, tested for SARS-CoV-2 because of suspected acute infections, and included SARS-CoV-2-positive and negative children. Children diagnosed or presumed to have multisystem inflammatory syndrome in children (MIS-C) were excluded from this analysis. Testing indications varied by institution and were modified as the pandemic evolved. Only those who underwent nucleic acid testing from the nasopharynx, nares, or throat were included in this analysis (ie, those who only underwent antibody testing were excluded given the low sensitivity of these tests during the acute illness)[12]. Those whose caregivers declined consent and children who declined assent, when appropriate, were excluded. Research ethics board approval was obtained at all participating institutions, with varying requirements for documentation of consent and assent (eg, verbal, electronic, and written).

At most study sites, research assistants received a list of all potentially eligible children daily along with their test results. At study initiation, nucleic acid testing capacity was limited, thus we attempted to recruit all children tested for SARS-CoV-2 infections. Over time, the number of children tested for SARS-CoV-2 increased. Therefore, the protocol was revised to have sites consecutively recruit all SARS-CoV-2-positive children and to sequentially contact test-negative children (starting with the first children tested each day) to a maximum of 5 children per day. As the positivity rate varied between sites, to

minimize sampling bias and promote similar proportions of test-positive participants across study sites, on September 8, 2020, the recruitment model was revised to have sites recruit all positive children along with two SARS-CoV-2 test-negative children from the same day for each positive child recruited (ie, 1:2 ratio).

DATA COLLECTION

Participant demographic, epidemiologic, chronic conditions/comorbidities, and clinical data were collected from caregivers shortly after the ED visit. Information was extracted from the medical record regarding the index ED visit and subsequent hospitalization, if required. Case report forms were modified as therapeutic considerations and our understanding of COVID-19 in children evolved. This led us to add data fields during the course of the study (eg, anosmia, ageusia); eTable 1. Study procedures were standardized through the use of a manual of operations. Data quality rules were programmed within RED-Cap, with data quality checks performed by the study statistician. Queries were issued for key variables that were missing, out of range or discrepant using REDCap's data resolution workflow.

SARS-CoV-2 TESTING & TREATMENT

This pragmatic observational study did not specify the approach to detection of SARS-CoV-2 infection. Local practices and illness severity dictated isolation, investigations, treatment, and hospitalization decisions.

SAMPLE SIZE

The PERN-COVID-19 prospective study intended to recruit up to 12,500 participants to acquire the 50+ COVID-positive children who experienced the study's primary objective.[11] When the target number of children experiencing the primary outcome had been recruited, no additional participants were enrolled. During planning of the parent study, we anticipated that the proposed target number of participants would provide sufficient precision for the current study, as reflected by the 95% confidence intervals.

STATISTICAL ANALYSIS

Continuous and categorical variables were summarized with medians and interquartile ranges and frequencies and percentages, respectively. For between-group comparisons, Cochran−Mantel−Haenszel and van Elteren tests stratified by study site were used for categorical and continuous variables, respectively. Predictors of corticosteroid administration were evaluated in all study participants, and in an a priori subgroup of those who were hospitalized, using multivariable conditional logistic regression, with the study site variable used to form the matched sets of observations.[13] The dependent variable (corticosteroids − oral, or intravenous) was limited to administration in the ED, hospital, or prescribed at ED discharge (ie, administration prior to the ED visit was excluded). The following independent variables were included in the model −

SARS-CoV-2 nucleic acid result, age, time-period (ie, each month identified chronologically), history of asthma, other chronic conditions/comorbidities, and wheezing on ED examination. In the model with all participants, we included hospitalization as a covariate; in the hospitalized participant analysis, we included intensive care unit (ICU) admission as a covariate. Children admitted to an observation unit were classified as 'hospitalized.' In both models, we included interaction terms between SARS-CoV-2 test results and study time period. As corticosteroids are routinely administered to children with asthma, we performed a sensitivity analysis excluding those with a history of asthma and those who were diagnosed as having an asthma exacerbation, wheeze, or reactive airways disease to allow for a focused assessment of corticosteroid use in COVID-19 disease. No correction for multiple pairwise comparisons was performed because of the exploratory nature of the study. Because only 1% of participants had missing data related to key variables, missing data were not imputed (eTable 2 in the Supplement). Statistical significance was designated as $P < .05$ (2-sided). Analyses were performed using SPSS 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and Stata 15.0 (College Station, TX: StataCorp LLC).

RESULTS

We enrolled 10,315 children who met all study eligibility criteria were enrolled; Figure. SARS-CoV-2 nucleic acid testing was positive for 3121 (30.3%) study participants, with the proportion positive varying by geographic region and race and/or ethnicity; Table 1, eTables 3, and 4. Compared to test-negative children, SARS-CoV-2-positive children were more likely to have been febrile and have respiratory symptoms; eTable 5. While they more often reported ageusia and anosmia ($P < .001$), these symptoms were uncommon, reported by 6.8% (166/2444) and 6.5% (160/2444) of SARS-CoV-2 positive children, respectively. SARS-CoV-2-positive children were less likely to have an underlying medical condition and gastrointestinal symptoms; Table 1, eTables 5, and 6. Prior to the index ED visit, SARS-CoV-2-positive children were less likely to have received a corticosteroid, antibiotics, and ibuprofen (all $P < .001$; Table 2). Although SARS-CoV-2-positive children were less frequently hospitalized at the index ED visit (638/3121 [20.4%] vs 1780/7194 [24.7%]; $P < .001$), ICU admission did not differ between test-positive and negative children (90/3121 [2.9%] vs. 190/7194 [2.6%]; $P = .53$).

TREATMENTS BY SARS-CoV-2 STATUS

Few SARS-CoV-2-positive children received specific therapies including corticosteroids (219/3120; 7.0%), antivirals (43/3120; 1.4%), intravenous immunoglobulin (IVIG; 14/2518; 0.6%), and convalescent plasma (4/2518; 0.2%); Table 3. Although corticosteroid use was less
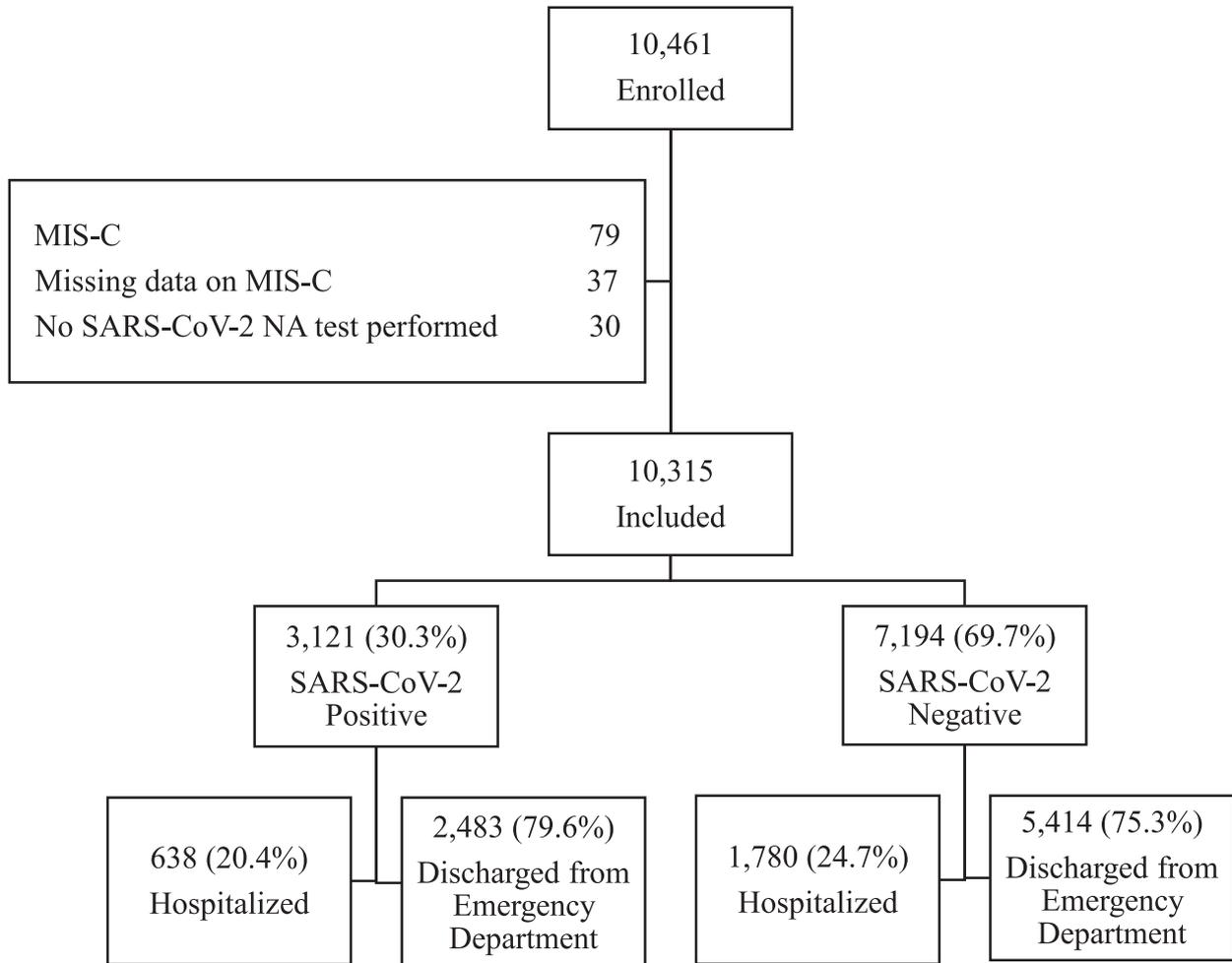
Figure. *Study participants. NA, Nucleic Acid; MIS-C, Multisystem inflammatory syndrome in children.*

common among SARS-CoV-2-positive, compared with test-negative children (219/3120 [7.0%] vs 759/7190 [10.6%]; *P* < .001), usage was more frequent among SARS-CoV-2 positive children who experienced severe outcomes (38/89 [42.7%] vs 180/3017 [6.0%]; *P* < .001). Similar proportions of SARS-CoV-2-positive and negative children received antiviral medications except for remdesivir which was more frequently administered to SARS-CoV-2-positive children (25/3120 [0.8%] vs 1/7188 [0.01%]; *P* = .001), particularly those who experienced severe outcomes (18/89 [20.2%]). Antibiotics were less commonly administered to SARS-CoV-2 test-positive children (396/3120 [12.7%] vs 1138/7192 [15.8%]; *P* < .001); Table 3, eTable 7.

Treatments by SARS-CoV-2 Status in Hospitalized Participants

Among hospitalized children, medications administered included corticosteroids (507/2416; 21.0%), antivirals (88/2416; 3.6%), and IVIG (31/1515; 2.0%); Table 4. Corticosteroid use was less frequent in SARS-CoV-2 test-positive compared with test-negative children (110/637 [17.3%] vs 397/1779 [22.3%]; *P* = .04). When comparing only children without histories of asthma or wheezing on examination, there was no difference in corticosteroid use between

those who were SARS-CoV-2 test-positive (49/487 [10.1%]) and test-negative (131/1273 [10.3%]); *P* = .90, eTable 8, and eFigure 1 in the Supplement. Remdesivir was administered almost exclusively to SARS-CoV-2-positive children ([25/637 {3.9%}] vs 1/1779 [0.1%]; *P* = .001); Table 4. While albuterol use was less common among SARS-CoV-2-positive hospitalized children ([88/609 {14.4%}] vs 350/1734 [20.2%]; *P* = .001), the use of respiratory ([148/608 {24.3%}] vs 376/1735 [21.7%]; *P* = .53] and inotropic support ([20/603 {3.3%}] vs 27/1730 [1.6%]; *P* = .09) did not differ between groups.

Corticosteroid Administration

SARS-CoV-2 detection was not associated with corticosteroid administration (aOR: 0.58 [0.27, 1.26]); Table 5. In the full participant analysis, corticosteroid administration was associated with age, history of asthma and other chronic conditions/comorbidities, wheezing on examination, and hospitalization. In the subgroup of hospitalized children, the same variables, except for chronic conditions/comorbidities, remained associated with corticosteroid use while SARS-CoV-2 detection was not associated with corticosteroid use (aOR: 0.65 [0.23, 1.84]). Sensitivity analysis excluding participants with histories of asthma and those diagnosed as having an asthma

Table 1. Demographic and Clinical Characteristics of Study Participants Based on Hospitalization and SARS-CoV-2 Test Result Status

	All Study Participants			Hospitalized Study Participants		
	SARS-CoV-2 Positive N = 3121	SARS-CoV-2 Negative N = 7194	P Value	SARS-CoV-2 Positive N = 638	SARS-CoV-2 Negative N = 1780	P Value
Demographic Characteristics						
Age[†]						
<60 Days, n (%)	147/3121 (4.7)	206/7194 (2.9)	<.001	72/638 (11.3)	120/1780 (6.7)	<.001
60 Days− < 2 Years, n (%)	1066/3121 (34.2)	2553/7194 (35.5)	.20	157/638 (24.6)	452/1780 (25.4)	.02
2 Years− < 5 Years, n (%)	529/3121 (16.9)	1619/7194 (22.5)	<.001	102/638 (16.0)	308/1780 (17.3)	.16
5 Years− <12 Years, n (%)	754/3121 (24.2)	1787/7194 (24.8)	.48	146/638 (22.9)	492/1780 (27.6)	.06
12 Years− <18 Years, n (%)	625/3121 (20.0)	1029/7194 (14.3)	<.001	161/638 (25.2)	408/1780 (22.9)	.002
Male sex, n (%)	1630/3121 (52.2)	3865/7194 (53.7)	.15	348/638 (54.5)	982/1780 (55.2)	.39
Underlying Medical Condition, n (%)	471/3118 (15.1)	1509/7178 (21.0)	<.001	177/637 (27.8)	586/1779 (32.9)	.77
Race, Self-Reported, US Only, n (%)						
American Indian or Alaska Native	9/1974 (0.5)	12/3490 (0.3)	.65	2/372 (0.5)	1/1201 (0.1)	.18
Asian	51/1974 (2.6)	108/3490 (3.1)	.32	8/372 (2.2)	39/1201 (3.9)	.12
Black or African American	695/1974 (35.2)	911/3490 (26.1)	<.001	103/372 (27.7)	289/1201 (24.1)	.73
Hispanic or Latino	694/1974 (35.2)	680/3490 (19.5)	<.001	106/372 (28.5)	180/1201 (15.0)	<.001
Native Hawaiian or Other Pacific Islander	12/1974 (0.6)	7/3490 (0.2)	.02	2/372 (0.5)	3/1201 (0.2)	.41
White	319/1974 (16.2)	1357/3490 (38.9)	<.001	104/372 (28.0)	568/1201 (47.3)	<.001
Other or mixed	194/1974 (9.8)	415/3490 (11.9)	.02	47/372 (12.6)	121/1201 (10.1)	.44
Enrolment Period						
March−May 2020, n (%)	218/3121 (7.0)	1996/7194 (27.7)	<.001	63/638 (9.9)	574/1780 (32.2)	<.001
June−August 2020, n (%)	842/3121 (27.0)	2807/7194 (39.0)	<.001	189/638 (29.6)	781/1780 (43.9)	.001
September−November, n (%)	751/3121 (24.1)	918/7194 (12.8)	<.001	148/638 (23.2)	195/1780 (11.0)	<.001
December 2020−February 2021, n (%)	753/3121 (24.1)	768/7194 (10.7)	<.001	142/638 (22.3)	137/1780 (7.7)	<.001
March 2021−June 2021, n (%)	557/3121 (17.8)	705/7194 (9.8)	<.001	96/638 (15.0)	93/1780 (5.2)	.004
Emergency Department Clinical Examination						
Triage Temperature, °C, Median (IQR)	37.1 (36.7, 37.8) N = 3069	37.1 (36.7, 37.9) N = 7105	.97	37.1 (36.7, 38.0) N = 626	37.0 (36.7, 37.6) N = 1757	.15
Triage Heart Rate, beats/minute, Median (IQR)	122 (102, 145) N = 3024	126 (104, 148) N=7051	.002	126 (106, 150) N = 621	125 (102, 149) N = 1742	.22
Triage Respiratory Rate, Breaths/Minute, Median (IQR)	26 (20, 33) N = 2882	26 (22, 34) N = 6825	<.001	26 (22, 36) N = 591	26 (20, 36) N = 1670	.09
Triage Oxygen Saturation, Room Air, Median (IQR)	98 (97, 100) N = 2792	98 (97, 100) N = 6341	<.001	98 (97, 100) N = 569	98 (97, 100) N = 1562	.002
Altered mental state (including obtunded, not easily arousable, confused, inappropriately agitated, unconscious), n (%)	37/3103 (1.2)	112/7173 (1.6)	.39	29/631 (4.6)	81/1776 (4.6)	.82
Crackles on examination, n (%)	46/3103 (1.5)	164/7180 (2.3)	.03	24/631 (3.8)	87/1775 (4.9)	.12
Wheezing on examination, n (%)	80/3103 (2.6)	493/7181 (6.9)	<.001	37/631 (5.9)	211/1776 (11.9)	<.001
Radiographic Imaging						
Chest radiographs performed while in ED, n (%)	553/3118 (17.7)	1201/7192 (16.7)	.12	279/638 (43.7)	539/1780 (30.3)	.15
Radiographic Pneumonia while in ED, n (%)	149/550 (27.1)	319/1196 (26.7)	.35	103/279 (36.9)	196/536 (36.6)	.11

Column percentages are reported.

ED indicates Emergency Department.

The P-values were obtained from Cochran−Mantel−Haenszel tests stratified by study sites for categorical variables, and van Elteren tests stratified by study sites for continuous variables as appropriate.

Radiographic Pneumonia definition: interstitial infiltrates/perihilar opacity, cavitation/abscess/pneumatocele, probable or definite pneumonia/consolidation, linear/streak opacity, pleural effusion.

†Age was collected in whole numbers for those >1 year of age.

Table 2. Prehospital Visit Therapies Administered, Including Children (and Treatments Provided) Transferred to the Study Institution. All Cells Represent n (%)

	SARS-CoV-2 Positive N = 3121	SARS-CoV-2 Negative N = 7194	P Value	Admitted N = 2418	Discharged N = 7897	P Value
Any Antiviral[†]	2/3113 (0.1)	6/7169 (0.1)	.51	6/2416 (0.2)	2/7866 (0.03)	.02
Any Corticosteroid	65/3096 (2.1)	293/7135 (4.1)	<.001	131/2400 (5.5)	227/7831 (2.9)	<.001
Oral	31/3096 (1.0)	104/7135 (1.5)	.46	72/2400 (3.0)	63/7831 (0.8)	<.001
Intravenous	2/3096 (0.1)	14/7135 (0.2)	.03	13/2400 (0.5)	3/7831 (0.04)	<.001
Inhaled	32/3096 (1.0)	175/7135 (2.5)	<.001	46/2400 (1.9)	161/7831 (2.1)	.04
Intramuscular	0/3096 (0)	3/7135 (0.04)	n/a	3/2400 (0.1)	0/7831 (0)	n/a
Any Antibiotic	91/3113 (2.9)	429/7171 (6.0)	<.001	225/2416 (9.3)	295/7868 (3.7)	<.001
Amoxicillin	29/3113 (0.9)	151/7171 (2.1)	<.001	46/2416 (1.9)	134/7868 (1.7)	.08
Antipyretics	1511/3113 (48.5)	3863/7173 (53.9)	.32	1034/2415 (42.8)	4340/7871 (55.1)	<.001
Acetaminophen	1184/3111 (38.1)	3116/7168 (43.5)	.30	801/2411 (33.2)	3499/7868 (44.5)	.003
Ibuprofen	592/3110 (19.0)	1833/7169 (25.6)	<.001	500/2412 (20.7)	1925/7867 (24.5)	.66
Salicylate	20/3112 (0.6)	35/7170 (0.5)	.56	24/2415 (1.0)	31/7867 (0.4)	.02

The P-values were obtained from Cochran−Mantel−Haenszel tests stratified by study sites.
n/a not estimable by Cochran−Mantel−Haenszel test.
†Includes acyclovir, oseltamivir, valganciclovir.

exacerbations, wheeze, or reactive airways disease did not alter the findings; eTable 9 in the Supplement.

DISCUSSION

Our multinational study revealed that although SARS-CoV-2 test-positive children receive a variety of treatments, no therapies are consistently administered, either to inpatients or outpatients. Corticosteroid administration, the most evidence-based treatment in SARS-CoV-2 infected adults, was not independently associated with SARS-CoV-2 test status, even among hospitalized children and after excluding children with asthma (history or active disease). Although infrequently provided, several treatments were administered more commonly to SARS-CoV-2 test-positive children including remdesivir, hydroxychloroquine, IVIG, and inotropic drugs.

Based primarily on the results of the RECOVERY trial which reported reduced mortality at 28 days associated with dexamethasone treatment of SARS-CoV-2 infected adults who were hospitalized and on supplemental oxygen or receiving mechanical ventilation,[9] corticosteroids are recommended for use in adults with severe COVID-19.[14,15] Consequently, dexamethasone use among hospitalized adults with COVID-19 has become routine.[16,17] Although the RECOVERY trial was modified (Version 5) to include children with respiratory COVID-19 infections,[18] few children have been enrolled and no conclusive evidence exists regarding corticosteroid use in this population. In our study, we found no independent association between corticosteroid use and SARS-CoV-2 status among hospitalized children including those admitted to the ICU. Corticosteroid use was associated with hospitalization, ICU admission (usage increasing in those more unwell), history of asthma, and the presence of wheeze. Thus, corticosteroid administration was likely performed to treat asthma and not SARS-CoV-2 infection. Moreover, as we did not find evidence of interaction between SARS-CoV-2 test status and time, it does not appear that evidence from adult trials is leading to adoption in children.

Although remdesivir trials, which have included more than 13,500 adults, report that use improves clinical outcomes among hospitalized patients,[19] access and regulatory approval varies by country.[20] As was seen with dexamethasone, remdesivir usage among hospitalized adults has increased as reflected in data from the University of California medical centers where administration increased from 4.9% to 62.5% between June 1 and December 31, 2020.[16] Although pediatric pharmacokinetic data analyzing the association between drug dose, plasma exposure, and intracellular drug exposure remain unavailable, some groups have endorsed remdesivir for use in children with severe COVID-19[21] and case-series describing its use have emerged.[22] A systematic review estimates that remdesivir is administered to 6.6% of children with severe COVID-19.[23] In our study, only 22 of the 151 SARS-CoV-2-positive children requiring oxygen therapy (ie, severe COVID-19) received remdesivir (Table 2). The limited use of this treatment may reflect recruitment prior to the maturation of evidence, lack of pediatric data, limited access, and/or conflicting guidelines.

Monoclonal antibody treatments have recently received emergency use authorizations (EUA) with approved indications including children and newborns with COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization.[8] However, given the limited safety and efficacy data in children, the American Academy of Pediatrics recommends infectious disease consultation prior to use in children <12 years of age, and a North American expert panel recommended against the routine administration of monoclonal antibodies to children, including those identified in the EUA.[24]

The ramifications of excluding children from COVID-19 clinical trials has increased as the pandemic has evolved. As adult vaccination rates rise, children are increasingly bearing the burden of disease and are treated based on limited evidence often with off-label therapies approved for adults. While early in the pandemic young children were infrequently infected by SARS-CoV-2,[25] in our study nearly 80% of cases occurred in children

Table 3. Emergency Department, Observation Unit or In-Patient Therapies Administered. All Cells Represent n (%)

	All Participants			SARS-CoV-2 Positive Participants Only		
	SARS-CoV-2 Positive N = 3121	SARS-CoV-2 Negative N = 7194	P Value	Severe Outcome N = 89	No Severe Outcome N = 3018	P Value
Albuterol	142/3091 (4.6)	652/7145 (9.1)	<.001	31/87 (35.6)	110/2991 (3.7)	<.001
Any Antibiotic[†]	396/3120 (12.7)	1138/7192 (15.8)	<.001	60/89 (67.4)	334/3017 (11.1)	<.001
Antifungal agent	19/3119 (0.6)	54/7188 (0.8)	.72	5/88 (5.7)	14/3017 (0.5)	<.001
Antipyretics	1098/3120 (35.2)	2940/7190 (40.9)	.06	63/89 (70.8)	1031/3017 (34.2)	<.001
Acetaminophen	712/3120 (22.8)	2083/7190 (29.0)	.01	58/89 (65.2)	654/3017 (21.7)	<.001
Ibuprofen	560/3120 (17.9)	1588/7190 (22.1)	.05	23/89 (25.8)	533/3017 (17.7)	.02
Salicylate	16/3120 (0.5)	44/7190 (0.6)	.45	4/89 (4.5)	12/3017 (0.4)	<.001
Any Antiviral	43/3120 (1.4)	47/7188 (0.7)	<.001	22/89 (24.7)	21/3017 (0.7)	<.001
Remdesivir	25/3120 (0.8)	1/7188 (0.01)	.001	18/89 (20.2)	7/3017 (0.2)	<.001
Acyclovir	15/3120 (0.5)	40/7188 (0.6)	.72	4/89 (4.5)	11/3017 (0.4)	.001
Ganciclovir	1/3120 (0.03)	3/7188 (0.04)	.91	0/89 (0)	1/3017 (0.03)	n/a
Lopinavir/Ritonavir	1/3120 (0.03)	0/7188 (0)	n/a	0/89 (0)	1/3017 (0.03)	n/a
Oseltamivir	1/3120 (0.03)	2/7188 (0.03)	.80	0/89 (0)	1/3017 (0.03)	n/a
Palivizumab	0/3120 (0)	1/7188 (0.01)	n/a	0/89 (0)	0/3017 (0)	n/a
Anakinra	1/3115 (0.03)	3/7181 (0.4)	.93	0/89 (0)	1/3012 (0.03)	n/a
Infliximab	0/3115 (0)	1/7181 (0.01)	n/a	0/89 (0)	0/3012 (0)	n/a
Any Corticosteroid	219/3120 (7.0)	759/7190 (10.6)	<.001	38/89 (42.7)	180/3017 (6.0)	<.001
Inhaled	18/3120 (0.6)	106/7190 (1.5)	.001	3/89 (3.4)	15/3017 (0.5)	.005
Intravenous	61/3120 (2.0)	174/7190 (2.4)	.03	27/89 (30.3)	34/3017 (1.1)	<.001
Oral	147/3120 (4.7)	505/7190 (7.0)	.02	13/89 (14.6)	133/3017 (4.4)	<.001
Convalescent Plasma*	4/2518 (0.2)	2/4643 (0.04)	.27	2/71 (2.8)	2/2435 (0.1)	.02
ECMO	0/3083 (0)	2/7142 (0.03)	n/a	0/85 (0)	0/2985 (0)	n/a
Hydration						
Intravenous fluids	569/3121 (18.2)	1524/7192 (21.2)	<.001	66/89 (74.2)	503/3018 (16.7)	<.001
Nasogastric fluids	17/3121 (0.5)	53/7191 (0.7)	.09	7/89 (7.9)	10/3018 (0.3)	<.001
Hydroxychloroquine	8/3120 (0.3)	4/7190 (0.1)	.03	2/89 (2.2)	6/3017 (0.2)	.07
Hypertonic Saline	12/3085 (0.4)	49/7142 (0.7)	.17	4/86 (4.7)	8/29986 (0.3)	<.001
Intravenous Immunoglobulin*	14/2518 (0.6)	17/4644 (0.4)[‡]	.67	10/71 (14.1)	4/2435 (0.2)	<.001
Inotropic support	19/3085 (0.6)	28/7141 (0.4)	.47	19/87 (21.8)	0/2985 (0)	n/a
Oxygen and Respiratory Support, Any	151/3090 (4.9)	402/7146 (5.6)	.002	64/89 (71.9)	86/2988 (2.9)	<.001
CPAP	6/3090 (0.2)	13/7146 (0.2)	.71	6/89 (6.7)	0/2988 (0)	n/a
BiPAP	12/3090 (0.4)	21/7146 (0.3)	.65	12/89 (13.5)	0/2988 (0)	n/a
Endotracheal Intubation/LMA	22/3090 (0.7)	43/7146 (0.6)	.98	22/89 (24.7)	0/2988 (0)	n/a
Renal Replacement Therapy	1/3085 (0.03)	11/7142 (0.2)	.16	1/86 (1.2)	0/2986 (0)	n/a

CPAP indicates Continuous Positive Airway Pressure; BiPAP, Bilevel Positive Airway Pressure; and ECMO, Extracorporeal Membrane Oxygenation.

The P-values were obtained from Cochran−Mantel−Haenszel tests stratified by study sites.

n/a not estimable by Cochran−Mantel−Haenszel test.

*Data field added to survey after study launch.

†For more detailed antibiotic usage – see Supplementary Table 5.

‡Of the 17 SARS-CoV-2 test-negative administered intravenous immunoglobulin, 13 with Kawasaki Disease, one with Idiopathic Thrombocytopenia Purpura, on with encephalitis, one with scarlet fever, and one child had acute inflammatory demyelinating polyneuropathy. None of these children had SARS-CoV-2 antibody testing performed.

<12 years of age. The latter finding is in keeping with an international network cohort study that used real-world data from European primary care records, South Korean and US insurance claims, and hospital databases to conclude that most COVID-19 diagnoses occur among children aged <4 years of age.[6] This finding highlights the importance of closing the gap which continues to expand, with evidence regarding the care of adults, particularly those who are critically ill continuously increasing, while progress in pediatric treatments lags and remains limited. A bibliographic analysis identified no pediatric interventional studies and few articles regarding therapeutics.[26] Of the initial 275 COVID-19 interventional clinical trials registered on ClinicalTrials.gov, only 30 (11%) were open to patients <18 years old.[27] In January 2021, the situation remained unchanged, with <10% of registered interventional COVID-19 trials including children.[18]

The lack of regulatory authorization and high-quality data to guide therapeutic management of children is not a new problem. In the United States, the proportion of medications prescribed to children that are off-label ranges from 62% to 85%.[28−30] In 2003, the Pediatric Research Equity Act was signed into law in the United States, with the goal of ensuring earlier access to information on drug approvals for children. Although only 34% of pediatric postmarketing studies mandated by the Pediatric Research Equity Act had been completed after 7 years of follow-up,[31] the COVID pandemic and has highlighted the failure of this law to achieve its aims.

Novel approaches are needed to generate the data to inform the care of children. Bayesian designs can permit

Table 4. Unadjusted Odds of Emergency Department, Observation Unit or Inpatient Therapies Administered to Hospitalized Children With a Positive SARS-CoV-2 Test Result

	SARS-CoV-2 Positive; N = 638	SARS-CoV-2 Negative; N = 1780	Unadjusted OR (95%CI)	P Value
Albuterol	88/609 (14.4)	350/1734 (20.2)	0.60 (0.45, 0.81)	.001
Antibiotics[†]	317/637 (49.8)	857/1780 (48.1)	1.04 (0.84, 1.29)	.70
Any Antiviral[†]	42/637 (6.6)	46/1779 (2.6)	3.27 (1.93, 5.54)	<.001
Acyclovir	15/637 (2.4)	39/1779 (2.2)	1.60 (0.81, 3.14)	.17
Ganciclovir	1/637 (0.2)	3/1779 (0.2)	1.83 (0.15, 22.87)	.64
Lopinavir/Ritonavir	1/637 (0.2)	0/1779 (0)	n/a	n/a
Oseltamivir	0/637 (0)	2/1779 (0.1)	n/a	n/a
Palivizumab	0/637 (0)	1/1779 (0.1)	n/a	n/a
Remdesivir	25/637 (3.9)	1/1779 (0.1)	21.11 (3.63, 122.59)	.001
Anakinra	1/635 (0.2)	3/1776 (0.2)	1.40 (0.13, 15.58)	.79
Infliximab	0/635 (0)	1/1776 (0)	n/a	n/a
Antifungal Agents	15/636 (2.4)	50/1779 (2.8)	1.03 (0.55, 1.94)	.93
Any Corticosteroid	110/637 (17.3)	397/1779 (22.3)	0.76 (0.58, 0.99)	.04
Inhaled	15/637 (2.4)	89/1779 (5.0)	0.54 (0.30, 0.97)	.04
Intravenous	56/637 (8.8)	157/1779 (8.8)	0.91 (0.63, 1.33)	.63
Oral	47/637 (7.4)	177/1779 (9.9)	0.81 (0.56, 1.18)	.28
Chest Drainage Procedure	5/602 (0.8)	7/1734 (0.4)	1.86 (0.49, 7.02)	.36
Convalescent Plasma*	4/492 (0.8)	2/1023 (0.2)	6.60 (0.62, 69.94)	.12
Extracorporeal Membrane Oxygenation	0/601 (0)	2/1731 (0.1)	n/a	n/a
Hydroxychloroquine	7/637 (1.1)	4/1779 (0.2)	6.30 (1.43, 27.70)	.02
Hypertonic Saline	8/603 (1.3)	40/1731 (2.3)	0.82 (0.36, 1.88)	.63
Inotropic Support	20/603 (3.3)	27/1730 (1.6)	1.85 (0.91, 3.77)	.09
Intravenous Immunoglobulin*	14/492 (2.8)	17/1023 (1.7)	1.12 (0.46, 2.70)	.81
Oxygen and Respiratory Support	148/608 (24.3)	376/1735 (21.7)	0.92 (0.71, 1.20)	.53
Continuous Positive Airway Pressure	6/608 (1.0)	13/1735 (0.7)	0.83 (0.26, 2.63)	.75
Bilevel Positive Airway Pressure	13/608 (2.1)	21/1735 (1.2)	1.39 (0.63, 3.04)	.41
Invasive ventilation by ETT/LMA	22/608 (3.6)	48/1735 (2.8)	0.97 (0.54, 1.75)	0.92
Renal Replacement Therapy	2/603 (0.3)	11/1731 (0.6)	0.65 (0.12, 3.45)	.61

ETT indicates Endotracheal Tube; LMA, Laryngeal Mask Airway.

The P-values and OR's were obtained from Cochran−Mantel−Haenszel tests stratified by study sites.

n/a not estimable by Cochran−Mantel−Haenszel test.

*Data field added to survey after study launch.

†Only those administered to >1.0% of any subgroup are specifically listed.

the use of historical adult data to generate a probability distribution to inform the design of pediatric trials which can integrate the adult data into the analytic plan, thereby reducing the required sample size.[32] Bayesian hierarchical modeling can also be used to combine data from simultaneously conducted adult and pediatric trials.[33] Such an approach can provide improved efficacy estimates in each population based on the similarity of effect. In the best case scenario, the effects are similar; if the effects are discordant, the adult estimate would have limited effect on that of the pediatric one.

Propensity matched designs are an alternative approach that can be used to examine and infer treatment effects when an adequately powered trial is not possible. However, since investigators have no control over treatment allocation in observational studies, confounding by indication may lead to misleading treatment effect estimates. To reduce the impact of confounding, propensity scores can be used to estimate the probability, based on pre-treatment characteristics, that a patient would receive the experimental treatment. The propensity score can be used to perform matching or stratification[34] and such analyses tend to produce treatment effects that are similar to randomized clinical trials.[35]

Our study has several limitations. We do not know why some children received certain treatments and others did not and we are unable to clearly evaluate if an intervention improved outcomes. We could not correlate intervention timing to clinician knowledge of SARS-CoV-2 test results as the latter data was not recorded. Delays in test turnaround time may have led to the empiric administration of COVID-specific treatments to children who were test-negative. This is particularly relevant to those enrolled in the early days of the pandemic, as there were often delays in the reporting of SARS-CoV-2 test results. We did not factor into our analysis the timing of availability of evidence supporting various interventions, the age range for which certain treatments are approved, and participant severity of illness which varied between participating centers based on testing policies. While study participants were matched based on day of testing and study site, no additional matching was performed to guide recruitment. Consequently, our SARS-CoV-2-positive and negative children differ in some characteristics. While several of these were adjusted for in our model, other confounders likely remain. The hospitalization rate in our study is higher than population estimates for COVID-19-infected children; this likely reflects the fact that children seeking ED care are more unwell than those seeking treatment at

Table 5. Multivariable Conditional Logistic Regression Model Matching by Study Site Evaluating Likelihood of Receiving an Oral or Intravenous Corticosteroid at the Index Emergency Department Visit, at Discharge, or During Hospitalization

	All Study Participants (N = 10237, Received = 906)[*]		Hospitalized at Index Visit (N = 2336, Received = 431)[†]	
	Odds Ratio (95%CI)	P-Value	Odds Ratio (95%CI)	P-Value
SARS-CoV-2 Nucleic Acid Test, Positive	0.58 (0.27, 1.26)	.17	0.65 (0.23, 1.84)	.41
Age Group				
<60 Days	0.17 (0.08, 0.39)	<.001	0.18 (0.08, 0.40)	<.001
60 Days - <2.0 Years	0.52 (0.40, 0.68)	<.001	0.34 (0.23, 0.51)	<.001
2.0 Years - <5.0 Years	1.32 (1.03, 1.70)	.03	1.23 (0.85, 1.78)	.28
5.0 Years - <12.0 Years	0.98 (0.77, 1.25)	.86	0.94 (0.68, 1.32)	.74
12.0 Years - <18.0 Years	reference		reference	
Month of Enrolment				
March−May 2020	Reference		Reference	
June−August 2020	1.07 (0.84, 1.37)	.60	1.01 (0.71, 1.43)	.95
September−November 2020	1.27 (0.91, 1.79)	.17	0.88 (0.52, 1.50)	.64
December 2020−February 2021	1.22 (0.85, 1.75)	.28	0.74 (0.40, 1.36)	.34
March−June 2021	1.33 (0.93, 1.90)	.13	0.52 (0.23, 1.17)	.11
History of Asthma, Yes	1.96 (1.61, 2.38)	<.001	1.55 (1.14, 2.11)	.005
Chronic Condition/Comorbidity (Excluding Asthma), Yes	1.27 (1.05, 1.53)	.01	1.01 (0.77, 1.31)	.97
Wheezing on History or Examination, Yes	12.2 (10.20, 14.59)	<0.001	8.91 (6.49, 12.23)	<.001
Hospitalized at the Index Visit, Yes	4.6 (3.79, 5.61)	<.001	N/A	
Intensive Care Unit Admission, Yes	N/A		2.46 (1.75, 3.45)	<.001
Interaction Terms				
Overall		.35		.12
SARS-CoV-2 positive × June to August 2020	1.31 (0.55, 3.10)	.54	0.95 (0.29, 3.11)	.93
SARS-CoV-2 positive × September to November 2020	1.60 (0.67, 3.81)	.29	2.28 (0.67, 7.73)	.19
SARS-CoV-2 positive × December 2020 to February 2021	1.53 (0.64, 3.70)	.34	1.93 (0.55, 6.86)	.31
SARS-CoV-2 positive × March to June 2021	2.18 (0.91, 5.24)	.08	3.17 (0.78, 12.93)	.11

N/A, the variable was not included in the regression model.

*2 sites (22 observations) dropped because of no steroid prescribed in these sites.

†5 sites (55 observations) dropped because of no steroid prescribed in these sites; 2 sites (15 observations) dropped because of all prescribed steroid in this site.

their primary care provider's office. Moreover, participating sites were predominantly tertiary care centers and some participants were transferred to these sites. Additionally, testing regimes varied between and within sites and over time. Early in the pandemic, SARS-CoV-2 testing was limited to the most unwell children. As the test positivity rate varied during the recruitment period, and between countries, our recruitment approach was modified to minimize its impact on our analytical inferences due to uneven recruitment between sites and countries. Further, to overcome confidentiality and privacy barriers associated with data sharing in an international study, we did not record data from potentially eligible children who declined to participate. Lastly, while we did record race for participants in Canada and the United States, due to the challenges of recording race separately for each of our European countries, those data were not collected.

In conclusion, we found that few SARS-CoV-2 infected children received any specific SARS-CoV-2 therapies. We found no independent association between corticosteroid use and SARS-CoV-2 test status in children, even among those hospitalized. Thus, there is an urgent need for research to include children to provide pediatric-specific data that can be used to guide the treatment of children who are now bearing a significant burden of COVID-19 disease.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.acap.2022.04.006.

REFERENCES

1. Centers for Disease Control and Prevention. Cases of coronavirus disease (COVID-19) in the U.S. Available at: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#demographics. Accessed December 17, 2021.

2. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html. Accessed August 6, 2021.

3. Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and disease severity of US children and adolescents diagnosed with COVID-19. JAMA Netw Open. 2021;4:e215298. https://doi.org/10.1001/jamanetworkopen.2021.5298. -e.

4. Kainth MK, Goenka PK, Williamson KA, et al. Northwell Health COVID-19 Research Consortium. Early experience of COVID-19 in a US Children's Hospital. Pediatrics. 2020;146:e2020003186. https://doi.org/10.1542/peds.2020-003186.

5. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr. 2020;174:e202430.

6. Duarte-Salles T, Vizcaya D, Pistillo A, et al. Thirty-day outcomes of children and adolescents with COVID-19: an international experience. Pediatrics. 2021;148:e2020042929. https://doi.org/10.1542/peds.2020-042929.

7. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ. 2020;370:m3249.

8. U.S. Food & Drug Administration. FDA expands authorization of two monoclonal antibodies for treatment and post-exposure prevention of COVID-19 to younger pediatric patients, including newborns. Available at: https://www.fda.gov/news-events/press-announcements/fda-expands-authorization-two-monoclonal-antibodies-treatment-and-post-exposure-prevention-covid-19. Accessed December 17, 2021.

9. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2020;384:693–704.

10. Chan K, Beck C, Chauvin-Kimoff L, et al. The acute management of paediatric coronavirus disease 2019 (COVID-19). Available at: https://www.cps.ca/en/documents/position/the-acute-management-of-paediatric-coronavirus-disease-2019covid-19. Accessed February 11, 2021.

11. Funk AL, Florin TA, Dalziel SR, et al. Prospective cohort study of children with suspected SARS-CoV-2 infection presenting to paediatric emergency departments: a Paediatric Emergency Research Networks (PERN) study protocol. BMJ Open. 2021;11:e042121.

12. Lisboa Bastos M, Tavaziva G, Abidi SK, et al. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. BMJ. 2020;370:m2516.

13. Breslow N. Covariance adjustment of relative-risk estimates in matched studies. Biometrics. 1982;38:661–672.

14. Nasa P, Azoulay E, Khanna AK, et al. Expert consensus statements for the management of COVID-19-related acute respiratory failure using a Delphi method. Crit Care. 2021;25:106.

15. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed December 17, 2021.

16. Watanabe JH, Kwon J, Nan B, et al. Medication use patterns in hospitalized patients with COVID-19 in California during the pandemic. JAMA Network Open. 2021;4:e2110775. -e.

17. Crothers K, DeFaccio R, Tate J, et al. Dexamethasone in hospitalised coronavirus-19 patients not on intensive respiratory support. Eur Respir J. 2021;2102532. https://doi.org/10.11183/13993003.02532-2021.

18. Fleming PF, Gale C, Molloy EJ, et al. Paediatric research in the times of COVID-19. Pediatr Res. 2021;90:267–271.

19. Lai CC, Chen CH, Wang CY, et al. Clinical efficacy and safety of remdesivir in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2021;76:1962–1968.

20. Hordijk L, Patnaik P. Covid-19: EU countries spent over €220m stockpiling remdesivir despite lack of effectiveness, finds investigation. BMJ. 2020;371:m4749.

21. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter Interim Guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. J Pediatric Infect Dis Soc. 2021;10:34–48.

22. Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate use of remdesivir in children with severe COVID-19. Pediatrics. 2021;147:e2020047803. https://doi.org/10.1542/peds.2020-047803.

23. Panda PK, Sharawat IK, Natarajan V, et al. COVID-19 treatment in children: a systematic review and meta-analysis. J Family Med Prim Care. 2021;10:3292–3302.

24. Wolf J, Abzug MJ, Wattier RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of coronavirus disease 2019 in children and adolescents. J Pediatric Infect Dis Soc. 2021;10:629–634.

25. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239–1242.

26. Stilwell PA, Munro APS, Basatemur E, et al. Bibliography of published COVID-19 in children literature. Arch Dis Child. 2021;107:168–172.

27. Hwang TJ, Randolph AG, Bourgeois FT. Inclusion of children in clinical trials of treatments for coronavirus disease 2019 (COVID-19). JAMA Pediatrics. 2020;174:825–826.

28. Bazzano AT, Mangione-Smith R, Schonlau M, et al. Off-label prescribing to children in the United States outpatient setting. *Acad Pediatr*. 2009;9:81–88.

29. Czaja AS, Reiter PD, Schultz ML, et al. Patterns of off-label prescribing in the pediatric intensive care unit and prioritizing future research. *J Pediatr Pharmacol Ther*. 2015;20:186–196.

30. Ivanovska V, Rademaker CMA, van Dijk L, et al. Pediatric drug formulations: a review of challenges and progress. *Pediatrics*. 2014;134:361–372.

31. Hwang TJ, Orenstein L, Kesselheim AS, et al. Completion rate and reporting of mandatory pediatric postmarketing studies under the US Pediatric Research Equity Act. *JAMA Pediatrics*. 2019;173:68–74.

32. Huff RA, Maca JD, Puri M, et al. Enhancing pediatric clinical trial feasibility through the use of Bayesian statistics. *Pediatr Res*. 2017;82:814–821.

33. McGlothlin AE, Viele K. Bayesian hierarchical models. *JAMA*. 2018;320:2365–2366.

34. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. *Eur Heart J*. 2011;32:1704–1708.

35. Kuss O, Legler T, Borgermann J. Treatments effects from randomized trials and propensity score analyses were similar in similar populations in an example from cardiac surgery. *J Clin Epidemiol*. 2011;64:1076–1084.