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MAJOR ARTICLE

Community-Onset Bacterial Coinfection in Children Critically Ill With Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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Background. Community-onset bacterial coinfection in adults hospitalized with coronavirus disease 2019 (COVID-19) is reportedly uncommon, though empiric antibiotic use has been high. However, data regarding empiric antibiotic use and bacterial coinfection in children with critical illness from COVID-19 are scarce.

Methods. We evaluated children and adolescents aged <19 years admitted to a pediatric intensive care or high-acuity unit for COVID-19 between March and December 2020. Based on qualifying microbiology results from the first 3 days of admission, we adjudicated whether patients had community-onset bacterial coinfection. We compared demographic and clinical characteristics of those who did and did not (1) receive antibiotics and (2) have bacterial coinfection early in admission. Using Poisson regression models, we assessed factors associated with these outcomes.

Results. Of the 532 patients, 63.3% received empiric antibiotics, but only 7.1% had bacterial coinfection, and only 3.0% had respiratory bacterial coinfection. In multivariable analyses, empiric antibiotics were more likely to be prescribed for immunocompromised patients (adjusted relative risk [aRR], 1.34 [95% confidence interval {CI}, 1.01–1.79]), those requiring any respiratory support except mechanical ventilation (aRR, 1.41 [95% CI, 1.05–1.90]), or those requiring invasive mechanical

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ventilation (aRR, 1.83 [95% CI, 1.36–2.47]) (compared with no respiratory support). The presence of a pulmonary comorbidity other than asthma (aRR, 2.31 [95% CI, 1.15–4.62]) was associated with bacterial coinfection.

Conclusions. Community-onset bacterial coinfection in children with critical COVID-19 is infrequent, but empiric antibiotics are commonly prescribed. These findings inform antimicrobial use and support rapid de-escalation when evaluation shows coinfection is unlikely.

Keywords. antimicrobial stewardship; bacterial coinfection; pediatric COVID-19; pneumonia; SARS-CoV-2.

While children are less likely than older individuals to develop severe illness from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), nearly 170 000 children aged <18 years have been hospitalized for SARS-CoV-2 in the United States (US) since 1 August 2020, and >1900 have died since 21 January 2021 [1]. The clinical presentation of severe COVID-19 often includes fever and respiratory distress, findings that can be difficult to distinguish from a serious bacterial infection, which may prompt use of empiric antibacterial agents early in hospitalization, especially in high-risk populations.

There is precedent to support early empiric treatment for bacterial coinfection in patients requiring hospitalization for severe respiratory viral illnesses, especially for those presenting with findings of septic shock or sepsis in congruence with the pediatric Surviving Sepsis Campaign guidelines [2, 3]. For example, influenza infection complicated by community-onset bacterial respiratory coinfection is not uncommon, and has been associated with more severe illness and poorer outcomes in hospitalized adults [4] and children [5]. In contrast, several adult studies have found low rates of community-onset coinfection in adult patients hospitalized with COVID-19 [6, 7], although rates of empiric antibiotic use were high. Such data in children are limited, and have combined pediatric hospitalizations for acute COVID-19 and multisystem inflammatory syndrome in children (MIS-C) [8], an entity that can present with clinical and laboratory findings distinct from acute COVID-19 infection. While several international studies have demonstrated increased rates of empiric antibiotic use in children hospitalized with COVID-19 related to illness severity [9, 10], data describing community-onset bacterial coinfection in children are lacking.

Using a national registry of pediatric COVID-19 hospitalizations that collected standardized clinical and laboratory data, we sought to characterize empiric antibiotic use, to understand the prevalence of community-onset bacterial coinfection in children hospitalized with critical illness from COVID-19, and to identify possible opportunities to encourage clinicians to de-escalate antibiotic use once bacterial sepsis has been ruled out in high-risk patients and patients presenting in shock. Therefore, we evaluated whether any clinical, laboratory, or radiographic features ascertainable at the time of admission were associated with use of empiric antibiotics or predictive of community-onset bacterial coinfection. Identification of clinical or laboratory findings that predict coinfection could inform decision making by clinicians caring for children hospitalized with COVID-19 and facilitate improved antimicrobial stewardship in this population.

METHODS

Study Cohort

We used data from the Overcoming COVID-19 Public Health Surveillance Registry. Overcoming COVID-19 is a nationwide active surveillance study enrolling patients <21 years old hospitalized with SARS-CoV-2 infection-related complications at >70 pediatric hospitals across 25 states [11]. Prospective patients were identified via screening for a positive SARS-CoV-2 test; patients may have been missed if their SARS-CoV-2 testing occurred at another institution prior to admission to the participating hospital. Data were not captured on the number of all SARS-CoV-2–positive pediatric intensive care unit (ICU) admissions at each hospital and thus the proportion of such patients included in the registry. The principal investigator at most sites was a critical care physician (investigators are listed in Supplementary Table 1). Our study included patients aged <19 years admitted to an ICU or high-acuity unit for pediatric intensive care from 15 March 2020 through 31 December 2020 with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR). Patients diagnosed with MIS-C, based on criteria established by the Centers for Disease Control and Prevention, were excluded [12]. The Overcoming COVID-19 registry was approved by the single institutional review board (IRB) at Boston Children's Hospital, and sites relied on the single IRB.

Data Collection

Cases were identified by site investigators and data were abstracted from electronic medical records into standardized REDCap (Research Electronic Data Capture) electronic case report forms (CRFs) [13, 14]. Data collected included demographics, signs and symptoms, comorbidities, laboratory and radiographic data, pharmacy data during admission including antimicrobials, and clinical course including respiratory and hemodynamic support required and outcomes. Data describing medications prescribed at discharge, including antibiotics, were not collected.

Outcomes

The first outcome assessed within our cohort was prescription of empiric antibiotics. To focus on those antibiotics intended to target community-onset bacterial infection, we included intravenous or enteral antibiotics administered within the first 48 hours of hospitalization. We included agents recommended by guidelines for community-acquired bacterial pneumonia in children [15] and those targeting other common bacterial respiratory pathogens, including methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*, as well as antibiotics used for nonrespiratory pathogens. We excluded azithromycin as this was often prescribed for possible antiviral effect on SARS-CoV-2 early in the pandemic. Antibiotic durations were ascertained from inpatient pharmacy data, but antibiotics prescribed at discharge were not included.

The next outcome assessed was presence of community-onset bacterial infection. To identify this cohort, we evaluated relevant CRF data from all subjects with a positive microbiological culture, PCR, or other nucleic acid amplification test within the first 3 days of hospitalization. Because, in accordance with pediatric Surviving Sepsis Campaign guidelines [3], critical care providers typically obtain blood cultures and cultures from other sites based on clinical suspicion (eg, endotracheal aspirate cultures in patients with respiratory failure) prior to initiation of empiric antibiotics, we presumed that microbiological testing was pursued in patients in whom coinfection was suspected. Conversely, we presumed that if microbiological testing was not performed, this was in most cases because the patient's providers had low suspicion for coinfection. Blood or respiratory culture results positive for organisms typically ascribed as contaminants were excluded [6]. Microbiologic serologic data were also excluded. Relevant data for further adjudication were compiled for each possible coinfection case, and these data were independently reviewed by 2 pediatric infectious diseases specialists (K. L. M. and M. M. N.). Criteria for coinfection (Supplementary Table 2) were determined a priori and adapted from previous literature [6, 7], and each adjudicator submitted their determinations separately. A third pediatric infectious diseases specialist (N. B. H.) reviewed and resolved any cases with discordant determinations.

Potential Predictors

To elucidate patient factors associated with empiric antibiotic initiation or presence of a community-onset bacterial coinfection, we considered demographic characteristics, including age, sex, and race/ethnicity. We also included social vulnerability index (SVI), extrapolated from the first 4 digits of a patient's zip code of residence. SVI is a score assigned to each census tract or county that ranges from 0 (low vulnerability) to 1 (high vulnerability), reflecting its rank on social factors (eg, poverty, lack of access to transportation, crowded housing) that affect a community's ability to cope with natural or human-caused disasters [16]. Because a 5-digit zip code would have permitted identification of some patients living in smaller rural areas, we collected only the first 4 digits of zip codes to maintain patient anonymity and confidentiality. We assessed certain underlying comorbidities using binary variables to indicate presence or absence of the comorbidity. These conditions included obesity (determined based on body mass index ≥95th percentile for age and sex for patients aged >2 years or selection as a comorbidity on the CRF); immunocompromise (defined as an immunologic, autoimmune, or oncologic condition or current use of immunosuppressive medications); asthma; non-asthma respiratory conditions (ie, chronic restrictive lung disease, tracheomalacia, bronchomalacia, bronchopulmonary dysplasia), and neurodevelopmental conditions. We evaluated features of the clinical presentation, including duration of fever and of symptoms more generally on presentation. As measures of illness severity on admission, particularly presence of acute respiratory failure and/or multiple organ system dysfunction (severe sepsis and/or shock), we assessed the level of respiratory support required (specified as invasive mechanical ventilation, respiratory support other than invasive mechanical ventilation [ie, noninvasive ventilation or high- or low-flow nasal cannula oxygen], or none) and the Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score [17]. Finally, we considered results of selected diagnostic studies, including abnormal findings on chest radiograph (CXR), as well as the highest white blood cell (WBC) count, C-reactive protein (CRP), and procalcitonin results on the day of admission.

Statistical Analyses

We used percentages to describe categorical variables and the median and interquartile range (IQR) to describe continuous variables (due to lack of normality). To evaluate univariable relationships between potential predictors and each outcome—empiric antibiotic use or presence of a community-onset bacterial coinfection—we used the χ^2 or Fisher exact test (for counts ≤5) for categorical predictors and the Kruskal-Wallis test for continuous predictors. We then built a 2-level mixed-effects Poisson regression model for each outcome with fixed effects for patient-level variables, including age and sex as prespecified covariates and hospital as a random effect, included to account for between-site heterogeneity. We selected as potential covariates for the multivariable models those variables that were associated with the outcome with $P \leq .30$ on univariable analyses. We chose a significance level of $P \leq .30$ for candidate variable selection to overcome power limitations due to the rarity of one of the outcomes of interest, bacterial coinfection, and thus reduce the risk of a type II error and improve sensitivity in identifying potential confounders [18, 19]. Collinearity of potential covariates was assessed using Pearson correlation coefficients and variance inflation factors prior to inclusion in the models. Variables were retained in the multivariable models if

their removal altered the full model effect estimate by ≥10% or if they were significantly associated with the outcome. The threshold used for statistical significance for all analyses was $P < .05$. We did not impute missing data. Analyses were performed using R 4.2.1 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Empiric Antibiotic Use

Of the >70 Overcoming COVID-19 Public Health Surveillance Registry sites, a total of 52 hospitals contributed patients to the cohort for this study (Supplementary Table 1). As shown in Table 1, 532 pediatric patients with severe or critical COVID-19 met criteria for evaluation, and the majority (63.3%) were prescribed empiric antibiotics. The most commonly prescribed antibiotics were ceftriaxone (40.6%) and vancomycin (28.4%), followed by cefepime (19.9%) (Table 2). Most patients received multiple antibiotics: 21.1% received 2, 10.0% received 3, and 18.4% received ≥4 antibiotics within the first 48 hours of hospitalization. More than one-third of subjects received ≥5 days of antibiotics despite the absence of evidence of bacterial coinfection (Table 3). There was no clear trend in the rate of antibiotic use over time as the pandemic progressed (Supplementary Figure 1). Prescribing differed across participating institutions, with the antibiotic use rate ranging from 13% to 100% (Supplementary Figure 2), but whether this was confounded by other variables (such as complexity of included patients by site) was not evaluated.

On unadjusted analyses, we found that empiric antibiotic use was not associated with age, sex, or race/ethnicity (Table 1). However, the median SVI was significantly higher among antibiotic recipients (0.541 [IQR, 0.407–0.670]) than nonrecipients (0.478 [IQR, 0.373–0.605]) ($P = .008$). Patients who were immunocompromised or had neurodevelopmental disorders ($P < .001$ for both conditions) were more likely to receive antibiotics. Antibiotic use was not associated with duration of fever or symptoms on presentation or with abnormalities on CXR; however, the majority of patients in both groups had abnormal radiographs as defined broadly by description of any abnormal findings. The median CRP was higher among antibiotic recipients (4.64 [IQR, 1.66–11.85] mg/dL) than nonrecipients (2.21 [IQR, 0.87–7.21] mg/dL) ($P = .0018$) when measured, as was the median procalcitonin (0.40 [IQR, 0.15–1.53] ng/mL vs 0.13 [IQR, 0.07–0.50] ng/mL; $P = .0018$), but the median WBC count did not differ significantly. Antibiotic recipients were more likely to require any respiratory support ($P < .001$). In addition, antibiotic use was associated with illness severity as reflected by higher median PELOD-2 scores on admission among antibiotic recipients (1 [IQR, 0–3]) than nonrecipients (0 [IQR, 0–2]) ($P < .001$).

On multivariable analysis, adjusting for age and sex, immunocompromise (adjusted relative risk [aRR], 1.34 [95% CI, 1.01–1.79]), but not neurodevelopmental conditions or non-asthma respiratory conditions, was independently associated with antibiotic use (Table 4). Compared with patients who needed no respiratory support, those requiring invasive mechanical ventilation (aRR, 1.83 [95% CI, 1.36–2.47]) or respiratory support other than mechanical ventilation (aRR, 1.41 [95% CI, 1.05–1.90]) were more likely to receive antibiotics. Antibiotic use was not associated with either demographic characteristics (age, sex, SVI) or admission PELOD-2 score. Although CRP and procalcitonin were significantly related to antibiotic use on univariable analysis, we were unable to evaluate these variables as potential covariates in multivariable models because each was reported for only a minority of the study cohort (44% for CRP and 22% for procalcitonin), and data were suspected to be missing not at random.

Community-Onset Coinfections

Of the 532 patients in the cohort, 333 had blood cultures (62.6%), 141 had respiratory cultures (26.5%), 200 had urine cultures (37.6%), 38 had cerebrospinal fluid cultures (7.1%), and 37 had cultures of another type (7.0%) sent within the first 3 days of hospitalization (Table 2). After exclusion of culture results reflecting contaminants, the remaining 99 cases (18.6%) were independently adjudicated by 2 reviewers to assess whether they met further criteria for coinfection. Of these, only 1 (1.0%) had discrepant determinations by 2 adjudicators, and a third independent adjudicator reviewed this case and deemed it be true coinfection. While not the focus of this study, co-detection of other respiratory viruses diagnosed by molecular methods was assessed if tested clinically at the site and was very infrequent; 3.4% of patients had rhinovirus/enterovirus coinfection, 1.1% had adenovirus, and single coinfections with influenza and respiratory syncytial virus (RSV) were detected.

In total, 38 patients (7.1%) were determined after expert adjudication to have true community-onset bacterial coinfection. As shown in Table 2, 13 (2.4%) of these were bloodstream infection, 16 (3.0%) were respiratory infection, 8 (1.5%) were urinary tract infection (UTI), and 4 were bacterial infections at various other sites (colitis, peritonitis from ruptured appendicitis, pharyngitis, and meningitis). Of the respiratory coinfections, 1 was proven, while 14 met criteria for possible and 1 for probable bacterial coinfection. As noted in the Methods, whether patients received empiric antibiotics for ≥5 days, which was part of the criteria used for probable or possible cases of bacterial respiratory coinfection (Supplementary Table 1), was ascertained solely from inpatient pharmacy data as information on discharge antibiotic prescriptions was not collected. However, of the 337 patients who received antibiotics, only 80 (23.7%) patients had hospital lengths of stay <5 days, and the

Table 1. Characteristics of Empiric Antibiotic Recipients and Nonrecipients

Clinical Characteristic	All Patients (N = 532)	Received Empiric Antibiotics (n = 337)	Did Not Receive Empiric Antibiotics (n = 195)	*P* Value
Age, y, median (IQR)	14.02 (5.53–17.29)	14.05 (5.67–17.38)	13.97 (4.92–17.21)	.62
Male sex	301 (56.6)	194 (57.6)	107 (54.9)	.61
Race/ethnicity[a]				
White, non-Hispanic	144 (27.1)	82 (24.3)	62 (31.8)	.29
Black, non-Hispanic	137 (25.8)	89 (26.4)	48 (24.6)	
Hispanic or Latino	196 (36.8)	131 (38.9)	65 (33.3)	
Other/unknown	55 (10.3)	35 (10.4)	20 (10.3)	
SVI, median (IQR)	0.516 (0.397–0.655)	0.541 (0.407–0.670)	0.478 (0.373–0.605)	.008
Comorbidities				
Obesity	194/436 (44.5)	131/283 (46.3)	63/153 (41.2)	.36
Immunosuppression	69 (13.0)	57 (16.9)	12 (6.2)	<.001
Asthma	106 (19.9)	70 (20.8)	36 (18.5)	.60
Nonasthma respiratory condition	83 (15.6)	59 (17.5)	24 (12.3)	.14
Neurodevelopmental	131 (24.6)	101 (30.0)	30 (15.4)	.001
Duration of illness, days, median (IQR)				
Duration of fever before presentation	2 (1–5)	2 (1–5)	3 (1–5)	.37
Duration of symptoms before presentation	2 (1–6)	2 (1–5)	3 (1–6)	.72
Highest level of respiratory support on admission				
None	148 (27.8)	65 (19.3)	83 (42.6)	<.001
Non-IMV[b] oxygen support	224 (42.1)	142 (42.1)	82 (42.1)	
IMV[b]	160 (30.1)	130 (38.6)	30 (15.4)	
Initial CXR findings				
Normal	65/392 (16.6)	43/288 (14.9)	22/104 (21.2)	.19
Abnormal	327/392 (83.4)	245/288 (85.1)	82/104 (78.8)	
Admission laboratory findings, median (IQR)				
WBC, K/μL[c]	8.20 (5.08–11.60)	8.06 (4.74–11.59)	8.55 (5.47–11.60)	.15
CRP, mg/dL[d]	4.37 (1.39–10.40)	4.64 (1.66–11.85)	2.21 (0.87–7.21)	.018
Procalcitonin, ng/mL[e]	0.30 (0.12–1.34)	0.40 (0.15–1.53)	0.13 (0.07–0.50)	.018
Severity score, median (IQR)				
PELOD-2 score	1 (0–3)	1 (0–3)	0 (0–2)	<.001
LOS, d				
ICU LOS, median (IQR)	4 (2–9)	5 (2–11)	3 (1–6)	.003
Hospital LOS, median (IQR)	7 (3–14)	9 (5–16)	5 (2–9)	<.001
Hospital LOS <5 d	174 (32.7)	80 (23.7)	94 (48.2)	<.001

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; CXR, chest radiograph; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; LOS, length of stay; PELOD-2, Pediatric Logistic Organ Dysfunction 2; SVI, social vulnerability index; WBC, white blood cell count.

[a]Race and ethnicity were abstracted from the patients' medical records.

[b]Fifteen patients received extracorporeal membrane oxygenation (13 receiving empiric antibiotics and 2 not receiving empiric antibiotics).

[c]Performed in 486 patients (320 receiving empiric antibiotics and 166 not receiving empiric antibiotics).

[d]Performed in 236 patients (184 receiving empiric antibiotics and 52 not receiving empiric antibiotics).

[e]Performed in 117 patients (96 receiving empiric antibiotics and 21 not receiving empiric antibiotics).

median hospital length of stay for the cohort was 9 days (IQR, 5–16) (Table 1), suggesting that the lack of postdischarge antibiotic data was unlikely to have resulted in misclassification of a substantial number of probable or possible bacterial respiratory coinfections. Three patients had multiple coinfections (1 with *Klebsiella* bacteremia and pseudomonal pneumonia, 1 with bacteremia and meningitis due to *Streptococcus agalactiae*, and 1 with bacteremia and UTI due to a gram-negative rod). No single pathogen predominated as causative of bacterial coinfection, though most respiratory coinfections were due to *P aeruginosa* and/or *S aureus*.

On unadjusted analyses, presence of a community-acquired bacterial coinfection was not associated with age, sex, race/ethnicity, or SVI (Table 3). Bacterial coinfection was significantly more common in patients with nonasthma respiratory conditions ($P = .01$) or neurodevelopmental conditions ($P = .005$) than patients without those conditions. Patients with bacterial coinfections did not differ significantly from those without coinfections in duration of fever or of symptoms on presentation but more often needed respiratory support ($P < .001$). Bacterial coinfection was not significantly associated with abnormal CXR findings or significant differences in

Table 2. Microbiologic Evaluation, Coinfections, and Antibiotic Use

Characteristic	All Patients (N = 532)
Cultures obtained within first 3 d of hospitalization	
Blood	333 (62.6)
Respiratory	141 (26.5)
Urine	200 (37.6)
Cerebrospinal fluid	38 (7.1)
Other (wound, fluid, or stool)	37 (7.0)
PCR testing performed	
Other respiratory viral PCR	300 (56.4)
Atypical bacterial PCR	1 (0.2)
Community-onset bacterial coinfections	
Any bacterial coinfection	38 (7.1)
Bloodstream	13 (2.4)
Klebsiella spp	3 (0.6)
MRSA	2 (0.4)
Pseudomonas aeruginosa	2 (0.4)
Other gram-negative rods	2 (0.4)
Escherichia coli	1 (0.2)
Candida albicans	1 (0.2)
Streptococcus agalactiae	1 (0.2)
Gram-positive cocci	1 (0.2)
Respiratory	16 (3.0)
P aeruginosa	6 (1.1)
MRSA	2 (0.4)
Methicillin-susceptible *S aureus*	2 (0.4)
MRSA and *P aeruginosa*	2 (0.4)
Enterobacter cloacae	1 (0.2)
Serratia marcescens	1 (0.2)
Streptococcus pneumoniae	1 (0.2)
Other gram-negative rods	1 (0.2)
Urinary tract	8 (1.5)
E coli	3 (0.6)
C albicans	2 (0.4)
E coli and *Pseudomonas*	1 (0.2)
S agalactiae	1 (0.2)
Other gram-negative rods	1 (0.2)
Colitis	1 (0.2)
Clostridioides difficile	1 (0.2)
Wound	1 (0.2)
Streptococcus anginosis and *Bacteroides fragilis* peritoneal fluid post–ruptured appendix	1 (0.2)
Streptococcus pyogenes pharyngitis	1 (0.2)
S agalactiae meningitis	1 (0.2)
Community-onset viral coinfection	
Rhinovirus/enterovirus	18 (3.4)
Adenovirus	6 (1.1)
Influenza A or B	1 (0.2)
Respiratory syncytial virus	1 (0.2)
Other	16 (3.0)
Empiric antibiotic therapy	
Ceftriaxone	216 (40.6)
Vancomycin	151 (28.4)
Cefepime	106 (19.9)
Ampicillin-sulbactam	36 (6.8)
Trimethoprim-sulfamethoxazole	34 (6.4)
Amoxicillin–clavulanic acid	30 (5.6)
Clindamycin	29 (5.5)
Piperacillin-tazobactam	29 (5.5)
Levofloxacin	26 (4.9)
Metronidazole	20 (3.8)
Linezolid	13 (2.4)
Doxycycline	11 (2.1)
Ciprofloxacin	9 (1.7)
Cefazolin	3 (0.6)
No. of antibiotics	
0	195 (36.7)
1	74 (13.9)
2	112 (21.1)
3	53 (10.0)
≥4	98 (18.4)

Data are presented as No. (%).

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction.

median WBC count, CRP, or procalcitonin. The median PELOD-2 score was higher in patients with coinfections (2.5 [IQR, 1–5]) than those without (0.5 [IQR, 0–2]) ($P < .001$), suggesting an association with degree of organ dysfunction.

On multivariable analysis, adjusting for age and sex, non-asthma respiratory conditions (aRR, 2.31 [95% CI, 1.15–4.62]) remained associated with bacterial coinfection (Table 5), as did a higher admission PELOD-2 score (for each 1-point increase, aRR, 1.18 [95% CI, 1.09–1.27]).

DISCUSSION

In a multicenter cohort of patients <19 years old admitted requiring pediatric intensive care for COVID-19 between 15 March 2020 and 31 December 2020, we found that microbiologically proven community-onset bacterial coinfections were infrequent, occurring in only 7.1% of patients. Nearly two-thirds of patients received empiric antibiotic therapy during the initial 48 hours of hospitalization, a rate that was consistent throughout the study period. Moreover, even among patients without evidence of a bacterial coinfection, more than one-third received antibiotics for a duration of 5 days or longer though guidelines support de-escalation of antibiotics for patients with acute COVID-19 when these criteria are met [2]. The rate of empiric antibiotic use varied widely across hospitals.

Only 3.0% of patients had proven respiratory coinfections due to bacterial pathogens, with the most commonly isolated organisms consisting of *P aeruginosa* and *S aureus* (both methicillin susceptible and resistant). Co-detection of respiratory viral pathogens was also relatively rare and similar to other studies of coinfection conducted during this period [6, 7],

Table 3. Characteristics of Patients With and Without Community-Onset Bacterial Coinfection

Clinical Characteristic	Confirmed Community-Onset Bacterial Coinfection (n = 38)	No Coinfection (n = 494)	*P* Value
Age, y, median (IQR)	14.49 (11.60–16.61)	14.01 (5.04–17.35)	.42
Male sex	24 (63.2)	277 (56.1)	.50
Race/ethnicity[a]			
White, non-Hispanic	11 (28.9)	133 (26.9)	.54
Black, non-Hispanic	12 (31.6)	125 (25.3)	
Hispanic or Latino	10 (26.3)	186 (37.7)	
Other/unknown	5 (13.2)	50 (10.1)	
SVI, median (IQR)	0.515 (0.397–0.654)	0.535 (0.398–0.715)	.26
Comorbidities			
Obesity	11/37 (29.7)	183/399 (45.9)	.09
Immunosuppressed	4 (10.5)	65 (13.2)	.80
Asthma	8 (21.1)	98 (19.8)	1.00
Nonasthma respiratory condition	17 (44.7)	114 (23.1)	.005
Neurodevelopmental	12 (31.6)	71 (14.4)	.01
Duration of illness, days, median (IQR)			
Duration of fever before presentation	1 (0.5–2.5)	2 (1–5)	.06
Duration of symptoms before presentation	2 (1–4)	3 (1–6)	.36
Highest level of respiratory support on admission			
None	8 (21.1)	140 (28.3)	<.001
Non-IMV[b] oxygen support	6 (15.8)	218 (44.1)	
IMV	24 (63.2)	136 (27.5)	
Initial CXR findings			
Normal	7/35 (20.0)	58/357 (16.2)	.74
Abnormal	28/35 (80.0)	299/357 (83.8)	
Admission laboratory findings, median (IQR)			
WBC, K/μL[c]	7.12 (3.62–10.30)	8.30 (5.15–11.65)	.19
CRP, mg/dL[d]	3.40 (1.82–7.12)	4.47 (1.25–10.73)	.88
Procalcitonin, ng/mL[e]	0.52 (0.17–10.78)	0.28 (0.12–1.34)	.44
Severity score, median (IQR)			
PELOD-2 score	2.5 (1–5)	0.5 (0–2)	<.001
Outcomes			
Duration of inpatient antibiotics, d, median (IQR)	12 (8–23)	5 (2–10)	<.001
Antibiotics ≥5 d	32 (84.2)	174 (35.2)	<.001
ICU LOS, d, median (IQR)	6 (3–16)	4 (2–8)	.06
Hospital LOS, d, median (IQR)	14 (7–29.5)	7 (3–14)	<.001
Hospital LOS <5 d	4 (10.5)	170 (34.4)	.002
Death	3 (7.9)	17 (3.4)	.16

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; CXR, chest radiograph; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; LOS, length of stay; PELOD-2, Pediatric Logistic Organ Dysfunction 2; SVI, social vulnerability index; WBC, white blood cells.

[a]Race and ethnicity were abstracted from the patient's medical record.

[b]Fifteen patients received extracorporeal membrane oxygenation (1 with a coinfection receiving empiric antibiotics and 14 without a coinfection).

[c]Performed in 486 patients (36 with a coinfection receiving empiric antibiotics and 450 without a coinfection).

[d]Performed in 236 patients (24 with a coinfection receiving empiric antibiotics and 212 without a coinfection).

[e]Performed in 117 patients (12 with a coinfection receiving empiric antibiotics and 105 without a coinfection).

with rhinovirus/enterovirus identified most commonly. This finding likely reflects low transmission rates of other respiratory pathogens during the study period. Bloodstream infections were reported in 2.4% of patients and were due to a variety of pathogens, including gram-negative organisms and methicillin-resistant *S aureus*. The remaining bacterial coinfections comprised a variety of clinical syndromes, including urinary tract infections and 1 case each of *Clostridioides difficile* colitis, *Streptococcus pyogenes* pharyngitis, and *Streptococcus agalactiae* meningitis, as well as a polymicrobial intraabdominal infection following appendiceal rupture. Whether SARS-CoV-2 infection predisposed to the latter infections is unclear; it is possible that some, while present concurrently, were unrelated to COVID-19.

In multivariable models, immunocompromised status and respiratory support requirement were associated with empiric antibiotic use, while only underlying nonasthma respiratory conditions and higher admission PELOD-2 scores were

Table 4. Characteristics Associated With Empiric Antibiotic Use

	Model With All Candidate Predictors[b]		Final Model[a]	
Variables in Final Model[a]	Adjusted RR (95% CI)	*P* Value	Adjusted RR (95% CI)	*P* Value
Age (continuous, per 1-y increase)	1.00 (.98–1.01)	.877	1.00 (.99–1.02)	.935
Female (reference = male)	1.00 (.80–1.24)	.996	0.99 (.80–1.23)	.947
Immunocompromised (reference =immunocompetent)	1.40 (1.05–1.88)	.024	1.34 (1.01–1.79)	.046
Respiratory support				
No support	Reference		Reference	
Support other than IMV	1.38 (1.03–1.87)	.033	1.41 (1.05–1.90)	.022
IMV	1.63 (1.14–2.34)	.008	1.83 (1.36–2.47)	<.001
Candidate predictors not retained in final model				
Race/ethnicity				
White, non-Hispanic	Reference		…	
Black, non-Hispanic	1.15 (.85–1.57)	.366	…	
Hispanic or Latino	1.23 (.93–1.64)	.149	…	
Other race/unknown	1.14 (.77–1.70)	.505	…	
SVI (continuous, per 0.1-unit increase)	1.04 (.98–1.10)	.240	…	
Any nonasthma respiratory condition (reference = not present)	0.98 (.71–1.34)	.895	…	
Any neurologic condition (reference = not present)	1.19 (.91–1.55)	.200	…	
Admission PELOD-2 score (continuous, per 1-point increase)	1.03 (.97–1.08)	.341	…	

Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; PELOD-2, Pediatric Logistic Organ Dysfunction 2; RR, relative risk; SVI, social vulnerability index.

[a]Variables were retained in the multivariable model if their removal altered the full model effect estimate by ≥10% or if they were significantly associated with the outcome.

[b]Variables were selected as potential covariates for the multivariable model if they were associated with the outcome with $P \leq .30$ on univariable analyses. Collinearity of potential covariates was assessed using Pearson correlation coefficients and variance inflation factors prior to inclusion in the models. Age and sex were included as prespecified variates, and hospital was included as a random effect to account for to account between-site heterogeneity.

associated with bacterial coinfection. The factors driving antibiotic use are understandable given the difficulty in attributing symptoms to severe COVID-19 versus potential coinfection early in hospitalization, especially in immunocompromised patients, yet we did not find higher rates of bacterial coinfection in immunocompromised patients in our study. Studies in adults with COVID-19 also have not identified higher rates of community-acquired bacterial coinfection in immunocompromised patients [6, 7], supporting a rationale for de-escalation of empiric antibiotics in these patients if diagnostic evaluation for coinfection is unrevealing. In univariable analyses, higher CRP and procalcitonin levels were associated with early antibiotic use but not with bacterial coinfection, though these biomarkers were not assessed in a majority of subjects and thus could not be evaluated in multivariable analyses. These biomarkers have similarly been found to lack sufficient specificity to distinguish early bacterial coinfection in adults hospitalized with COVID-19 [6, 7, 20].

An understanding of rates of bacterial coinfection in severe SARS-CoV-2 compared with other respiratory viruses could inform empiric antibiotic prescribing. One study comparing the patients in this cohort to children hospitalized with influenza-related illness found lower rates of respiratory (3.4% vs 10.1%) and bloodstream (2.9% vs 7.3%) coinfection despite a similar risk of critical illness and death [21]. A similar study in adults demonstrated a 3-fold lower rate of respiratory bacterial coinfection within 48 hours of intubation in patients with SARS-CoV-2 versus influenza infection [22]. Another study in adults found bacterial coinfection present upon admission in only 4% of those with SARS-CoV-2, compared to 27% with influenza and 29% with RSV [23]. In a study of children hospitalized with bronchiolitis largely due to RSV or rhinovirus, a bacterial pathogen was identified in 36% of respiratory specimens obtained at the time of intubation [24], though the role of bacterial coinfection in these patients' courses was not further described. Taken together, data available thus far suggest that community-acquired bacterial coinfection in children and adults is less common in severe or critical SARS-CoV-2 infection than in other respiratory viral infections with similarly severe courses.

Strengths of this study include enrollment of subjects from a large multicenter cohort representing geographic and institutional variability, robust standardized clinical and microbiologic data collection, and rigorous adjudication of coinfection cases conducted separately by multiple experts. One limitation of this study is inclusion of subjects prior to the emergence of the Delta, Omicron, and other variants of concern of SARS-CoV-2. Patterns of antibiotic use and coinfection with these variants remain to be studied. Furthermore, the nonpharmacologic measures implemented to reduce SARS-CoV-2 transmission during the period of this study contributed to lower transmission of other respiratory bacterial and viral infections [25, 26], further supporting the need to assess coinfections during other periods of the pandemic. In addition, during

Table 5. Characteristics Associated With Community-Acquired Bacterial Coinfections

	Model With All Candidate Predictors[b]		Final Model[a]	
Variables in Final Model[a]	Adjusted RR (95% CI)	*P* Value	Adjusted RR (95% CI)	*P* Value
Age (continuous, per 1-y increase)	1.04 (.99–1.10)	.101	1.04 (.99–1.10)	.101
Female (reference = male)	0.78 (.40–1.53)	.466	0.78 (.40–1.53)	.466
Any nonasthma respiratory condition (reference = not present)	2.02 (.88–4.67)	.099	2.31 (1.15–4.62)	.018
Admission PELOD-2 score (continuous, per 1-point increase)	1.09 (.98–1.21)	.126	1.18 (1.09–1.27)	<.001
Candidate predictors not retained in final model				
SVI (continuous, per 0.1-unit increase)	1.05 (.89–1.25)	.565	…	
Any neurologic condition (reference = not present)	1.24 (.56–2.76)	.593	…	
Obesity (reference = not present)	0.72 (.34–1.49)	.371	…	
Respiratory support				
No support	Reference		…	
Support other than IMV	0.41 (.14–1.22)	.109	…	
IMV	1.51 (.56–4.08)	.415	…	

Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; PELOD-2, Pediatric Logistic Organ Dysfunction 2; RR, relative risk; SVI, social vulnerability index.

[a]Variables were retained in the multivariable model if their removal altered the full model effect estimate by ≥10% or if they were significantly associated with the outcome.

[b]Variables were selected as potential covariates for the multivariable model if they were associated with the outcome with $P \leq .30$ on univariable analyses. Collinearity of potential covariates was assessed using Pearson correlation coefficients and variance inflation factors prior to inclusion in the models. Age and sex were included as prespecified variates, and hospital was included as a random effect to account for to account between-site heterogeneity.

the study period, SARS-CoV-2 testing availability and turnaround time evolved, which could have affected clinical decision making. Another limitation of this study is inclusion of only ICU and high-acuity unit patients. Since our findings identified higher severity scores and ICU-level respiratory support requirements as risk factors for bacterial coinfection, this suggests that coinfection rates in patients requiring lower levels of care may be even lower, but this should be confirmed. This was a public health surveillance registry, and not all critical COVID-19 patients may have been captured. Cultures may not have been collected for all patients prior to antibiotic initiation, but data on timing of cultures relative to antibiotics were not obtained. We did not collect information on institutional factors that may have influenced empiric antibiotic initiation or selection, such as clinical guidelines or order sets; however, to account more generally for between-site heterogeneity, we included hospital as a random effect in the multivariable model assessing predictors of empiric antibiotic use. Last, given the challenges in diagnosing pediatric bacterial pneumonia, respiratory coinfections may be undercounted in this cohort. Since only subjects with verified culture data were adjudicated, patients with probable or possible bacterial pneumonia with no qualifying culture data were missed. Non–SARS-CoV-2 respiratory viruses were variably tested, and co-detection may be underappreciated. Also, since we did not collect discharge medication data, a subject who otherwise met radiographic and/or clinical criteria would not have met criteria for respiratory coinfection, which included an antibiotic duration of ≥5 days (Supplementary Table 2), if they were discharged before day 5.

In conclusion, similar to findings in adults, empiric antibiotic use in children admitted with severe and critical COVID-19 infection is high and variable across centers, but the prevalence of community-onset bacterial coinfection in this population is likely low even in the sickest patients. Pediatric providers accustomed to caring for children hospitalized with other respiratory viruses should be aware that there may be a lower likelihood of bacterial coinfection with SARS-CoV-2 infection, even in children requiring pediatric intensive care. Empiric antibiotics are a critical component of early care in children who present with sepsis, including those with COVID-19, and the spectrum of coinfections confirmed in this cohort suggests that, when indicated, antibiotic choices based on institutional or national guidelines addressing the suspected clinical syndrome would be appropriate, with consideration given to patient risk factors for more resistant organisms. However, in keeping with the pediatric Surviving Sepsis Campaign guidelines, which state that "if no pathogen is identified, we recommend narrowing or stopping empiric antimicrobial therapy according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement" [3], de-escalation or discontinuation of empiric antibiotics should be encouraged for patients with COVID-19 after evaluation for bacterial coinfection and further assessment of the clinical course are reassuring.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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 (CDC).

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