Severe Coronavirus Bronchiolitis in the Pre–COVID-19 Era

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The first human coronaviruses, OC43 and 229E, were discovered in the 1960s, but NL63 and HKU1 were discovered in 2004 and 2005, respectively. These 4 endemic coronaviruses cause respiratory illness in hospitalized children,[1] as does the newest coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19).[2–4] Despite many SARS-CoV-2 publications, there remains limited information about viral coinfections and the importance of viral load to acute severity. Given the potential for useful insights into SARS-CoV-2 childhood infections, we analyzed data from 2 prospective multicenter cohorts of children hospitalized with bronchiolitis in the pre–COVID-19 era to examine endemic coronavirus bronchiolitis, specifically viral coinfections and the association between viral load and acute severity.

METHODS

As previously described,[5,6] we conducted the 30th Multicenter Airway Research Collaboration (MARC-30) and 35th Multicenter Airway Research Collaboration (MARC-35) studies during 2007–2010 and 2011–2014, respectively. Although both studies enrolled children hospitalized with bronchiolitis, MARC-30 enrolled children aged <2 years, and MARC-35 enrolled infants aged <1 year at sites across the United States. Both studies used similar protocols, were approved by the institutional review board, and excluded children with known heart and lung disease, immunodeficiency, immunosuppression, or gestational age <32 weeks.

In both studies, site teams conducted structured interviews, conducted medical record reviews, and collected nasopharyngeal aspirates within 24 hours of hospitalization. For both studies, the same laboratory used real-time reverse transcriptase polymerase chain reaction to test for the 4 endemic coronaviruses(OC43, 229E, NL63, and HKU1) and 14 other viruses, including respiratory syncytial virus (RSV).[5] Viral genomic load was quantified in MARC-35 by using the cycle threshold (Ct) value.

The current analysis is focused on children with solo RSV or coronavirus infection in the pre–COVID-19 era. After using descriptive statistics, we examined the differences in the risk of intensive care use (ie, positive pressure ventilation or intensive care admission) between solo RSV infection and RSV and coronavirus coinfection by constructing a generalized linear mixed model with logit link that adjusts for age and patient clustering within sites. To investigate the association of coronavirus genomic load with the severity outcome, we also fit a logistic regression model adjusting for age and RSV coinfection status. The covariates were selected on the basis of clinical plausibility and a priori knowledge.

RESULTS

Of 1880 children hospitalized with bronchiolitis in the analytic cohort, 219 (12%) had 1 of the 4 endemic coronaviruses. Although most patient

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Dr Mansbach conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Hasegawa conceptualized and designed the study, conducted the analyses, helped interpret the data, and critically revised the article for important intellectual content; Dr Piedra conceptualized the study, helped interpret the data, and critically revised the article for important intellectual content; Ms Sullivan conceptualized the study, coordinated and supervised data collection, and critically revised the article for important intellectual content; Dr Camargo conceptualized and designed the study, coordinated and supervised data collection, helped interpret the data, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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TABLE 1 Patient Characteristics and Respiratory Pathogens in Infants With Severe Bronchiolitis in 2 US Cohort Studies

Variable	Solo RSV Infection	Coronavirus Infection	*P*	Solo Coronavirus Infection	*P*
N	1661	219	—	32	—
Age, mo, median (IQR)	2.8 (1.4–5.8)	3.7 (1.9–7.2)	<.001	3.7 (1.7–6.0)	.44
Female sex, *n* (%)	705 (42)	70 (32)	.003	9 (28)	.15
Race and/or ethnicity, *n* (%)			.19		.45
Non-Hispanic white	690 (42)	96 (44)	—	17 (53)	—
Non-Hispanic Black	326 (20)	52 (24)	—	7 (22)	—
Hispanic	554 (33)	64 (29)	—	7 (22)	—
Other	91 (6)	7 (3)	—	1 (3)	—
Prematurity (gestational age <37 wk), *n* (%)	319 (19)	53 (24)	.09	7 (22)	.65
Clinical presentation					
Onset of symptoms <24 h, *n* (%)	67 (4)	15 (7)	.08	6 (19)	.002
Body wt, kg, median (IQR)	5.7 (4.4–7.6)	6.3 (4.7–8.1)	.006	5.8 (4.5–7.6)	.94
Wheezing on examination, *n* (%)	965 (60)	144 (66)	.06	19 (61)	.99
Apnea, *n* (%)	117 (9)	13 (7)	.49	1 (4)	.72
Clinical course					
Intensive care use, *n* (%)[a]	286 (17)	45 (21)	.22	6 (19)	.81
ICU admission, *n* (%)	275 (17)	44 (20)	.21	6 (19)	.81
Intubation and/or CPAP use, *n* (%)	112 (7)	20 (9)	.20	2 (6)	.99
Hospital length of stay, d, median (IQR)	2 (1–4)	2 (1–4)	.93	2 (1–2)	.01
Region, *n* (%)			.06		.22
Northeast	325 (20)	54 (25)	—	9 (28)	—
Midwest	271 (16)	45 (21)	—	8 (25)	—
South	690 (43)	76 (35)	—	11 (34)	—
West	375 (23)	44 (20)	—	4 (13)	—
Hospitalization month, *n* (%)			.15		.55
November	131 (8)	22 (10)	—	3 (9)	—
December	323 (1)	38 (1)	—	8 (25)	—
January	503 (3)	73 (33)	—	12 (38)	—
February	445 (27)	43 (20)	—	4 (13)	—
March	236 (14)	40 (18)	—	5 (16)	—
April	23 (1)	3 (1)	—	0 (0)	—
No. detected pathogens, median (IQR)	1 (1–1)	2 (2–3)	<.001	1 (1–1)	—
Detected pathogens, *n* (%)	—	—	—	—	.61
Coronavirus[b]					
OC43	0 (0)	74 (34)	—	14 (44)	—
229E	0 (0)	39 (18)	—	2 (6)	—
NL63	0 (0)	57 (26)	—	8 (25)	—
HKU1	0 (0)	57 (26)	—	9 (28)	—
Solo coronavirus infection	0 (0)	32 (15)	—	32 (100)	—
Adenovirus	0 (0)	17 (8)	—	0 (0)	—
Enterovirus	0 (0)	8 (4)	—	0 (0)	—
hMPV	0 (0)	24 (11)	—	0 (0)	—
Influenza virus[c]	0 (0)	3 (1)	—	0 (0)	—
Rhinovirus	0 (0)	43 (20)	—	0 (0)	—
RSV	1661 (100)	151 (69)	—	0 (0)	—
PIV[d]	0 (0)	7 (3)	—	0 (0)	—
Others[e]	0 (0)	7 (3)	—	0 (0)	—

Data are no. (%) of infants unless otherwise stated. Percentages may not equal 100 because of rounding. Differences in characteristics are tested with the χ^2 test, Fisher's exact test, or the Mann–Whitney *U* test, as appropriate. CPAP, continuous positive airway pressure; hMPV, human metapneumovirus; IQR, interquartile range; PIV, parainfluenza virus; —, not applicable.

[a] Admission to an ICU and/or use of positive pressure ventilation (invasive or noninvasive) during hospitalization for bronchiolitis.

[b] Eight with multiple coronaviruses.

[c] Includes influenza A and B and the 2009 novel H1N1.

[d] Includes PIV types 1, 2, and 3.

[e] Includes human bocavirus type 1, *Mycoplasma pneumoniae*, and *Bordetella pertussis*.

characteristics did not differ, compared with children with solo RSV infection, children with coronavirus bronchiolitis were older and more likely male (Table 1). Only 32 (15%) infections were solo coronavirus infections. The most common coinfecting virus was RSV (Table 1).

Among the 4 coronaviruses, there were no significant differences in patient characteristics, except for month of hospitalization (data not shown). In a multivariable model, compared with solo RSV infection, RSV and coronavirus coinfection did not have a significantly different risk of intensive care use (odds ratio 1.43;

95% confidence interval [CI] 0.94–2.18; $P = .10$). However, a higher genomic load of coronavirus (ie, lower Ct value) was associated with a higher risk of intensive care use (odds ratio 1.22 per 1-U decrease in Ct value; 95% CI 1.02–1.51; $P = .04$; Fig 1).

DISCUSSION

On the basis of 2 large prospective multicenter cohorts of children hospitalized with bronchiolitis in the pre–COVID-19 era, we found that 85% of endemic coronavirus bronchiolitis cases had a coinfecting virus. In other words, identifying RSV or another respiratory virus would not exclude the possibility of endemic coronavirus infection in children hospitalized for bronchiolitis. Although SARS-CoV-2 may interact with other respiratory viruses differently from these 4 endemic coronaviruses,[7] comprehensive virology data in children hospitalized with COVID-19 are lacking. Until SARS-CoV-2 testing is more rapid and widely available and false-negatives are better understood, the present results are a warning to clinicians currently caring for children with respiratory symptoms that identifying a common respiratory virus (eg, RSV or rhinovirus) does not exclude coinfection with SARS-CoV-2.[5]

Coinfection with endemic coronavirus was not associated with increased disease severity. However, similar to RSV and different from rhinovirus,[8,9] higher coronavirus viral load was associated with higher severity of illness. These viral load results suggest that antiviral agents may benefit children with endemic coronavirus bronchiolitis and possibly children with COVID-19.[10]

In 2 prospective multicenter cohorts of infants hospitalized with endemic coronavirus bronchiolitis, we found that viral coinfections are common and that higher viral load is associated with higher acute severity.

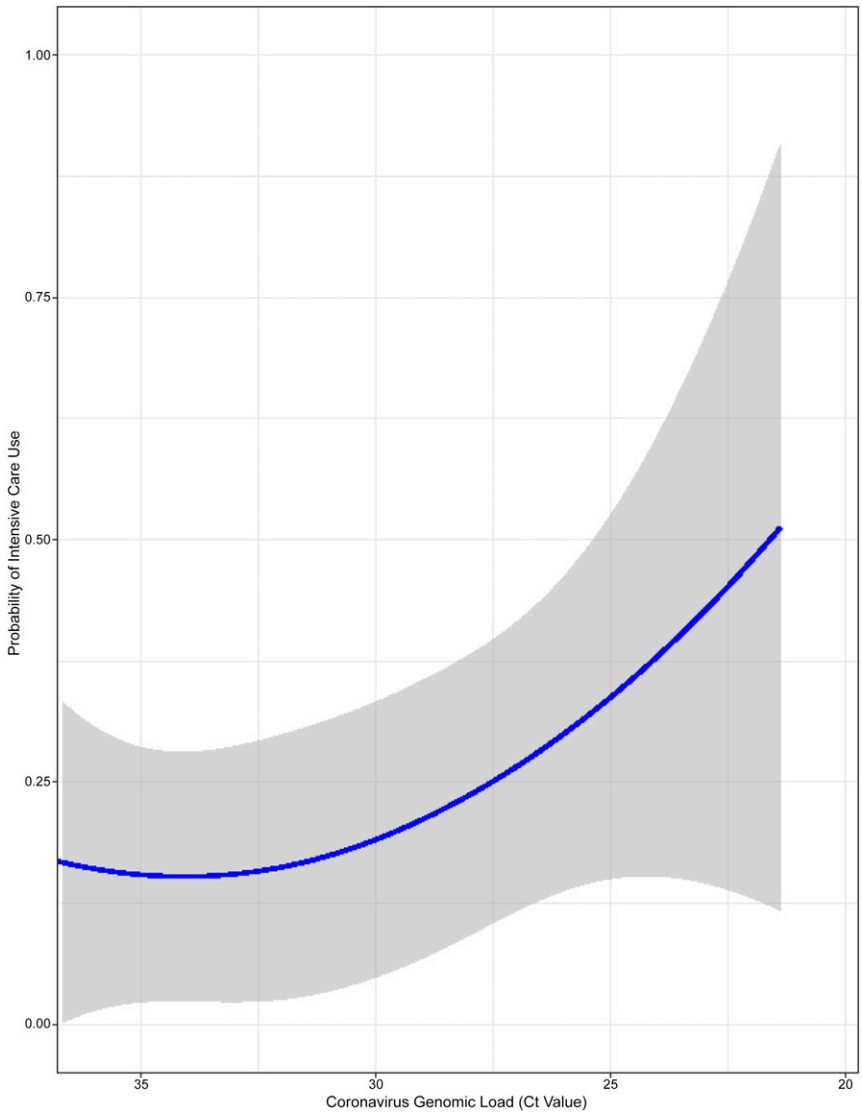

FIGURE 1

Association of coronavirus genomic load with risks of intensive care use in infants hospitalized for bronchiolitis. The fitted line represents the locally estimated scatterplot smoothed curve for infants with coronavirus bronchiolitis in MARC-35. There was a significant association of coronavirus genomic load (lower Ct value indicates higher genomic load) with a higher risk of intensive care use after adjustment for age and coinfection with RSV. The gray area represents the 95% CI.

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ABBREVIATIONS

CI: confidence interval
COVID-19: coronavirus disease 2019
Ct: cycle threshold
MARC-30: 30th Multicenter Airway Research Collaboration
MARC-35: 35th Multicenter Airway Research Collaboration
RSV: respiratory syncytial virus
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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