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Epidemiology, Disease Course and Outcome Comparison of Children Hospitalized with Single Versus Multiple Respiratory Viral Infections: A Single-Center Retrospective Cohort Study

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Abstract

Introduction: Respiratory viral infections cause a significant morbidity in children. Significance of isolation of multiple viruses in Acute Lower Respiratory Infections (ALRI) in children is not well characterized. The aim of this study was to compare demographics, resource utilization, and outcomes of patients with single versus multiple viral co-infections.

Methods: This retrospective study was conducted by reviewing electronic records of patients hospitalized with positive respiratory viral panel within 48 hours of admission from 1/1/2015 to 12/31/2019. Outcome assessment included resource utilization, length of stay and costs. Univariate and multivariable analysis were performed.

Results: A total of 2192 patients were included in this study. 16.4% of all patients had viral co-infections. Rhino/enterovirus comprised 49.2% of all identified viruses. Rhino/enterovirus and RSV were the most common co-infections (22.4%). Patients with coinfection were younger in age (median 11.3 months). Intravenous antibiotics were prescribed in 29.4% with no difference in usage among the two groups. Patients with viral coinfections had a higher rate of high flow nasal cannula utilization, intubation, and length of stay (3 days [1,5] vs 2 days [1,4]). Overall mortality rate of study population was 0.3% with no difference between the two groups. Cost of care was higher for patients with coinfection but not significant after adjusting for confounders.

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Conclusion: Children with viral coinfection comprise a sizeable proportion of hospitalized children with bronchiolitis and have a higher severity of illness as suggested by increased use of high flow nasal cannula and hospital length of stay.

Introduction

Acute Lower Respiratory Tract Infections (ALRI) are common diseases in pediatric patients and one of the leading causes of hospitalizations, with an estimated 149,000 admissions annually [1]. Most children present with mild-to-moderate illness, however, 2–6% of hospitalized patients require Pediatric Intensive Care Unit (PICU) admission [2]. Respiratory Syncytial Virus (RSV) is the commonest etiology associated with ALRI, accounting for 43–74% of all cases [3]. The widespread use of respiratory real-time multiplex Polymerase Chain Reaction [PCR] has helped in identifying other viruses including rhinovirus, coronavirus, human metapneumovirus, parainfluenza virus, and adenovirus [4,5].

Viral co-infection in hospitalized children with ALRI ranges from 10% to 40% [6,7]. The clinical implications of these viral co-infections remain controversial. Some studies have suggested that viral co-infection results in a more severe disease of ALRI, while others have reported that course and severity did not differ between infections caused by one or multiple viruses [8-10]. Several studies about viral co-infection were limited for only providing descriptive statistics without accounting for confounders or for having a small sample size [11,12]. It is essential to know if multiple respiratory viral infections lead to worse clinical outcomes, since early intensive care given to this population might decrease the complications. As we learn more about COVID 19 infestations in children it would be helpful to have contemporary data on impact of other viral coinfection is on the disease progression, so the impact of COVID 19 coinfection with other common respiratory viruses in children can be compared.

This retrospective study was designed to compare the demographics, disease distribution, resource utilization and outcomes of children with single versus multiple viral coinfections.

Methods

After Institutional Review Board (IRB) approval, we identified all patients (0 to 17 years of age) who were admitted to the Children's Hospital of Illinois from 01/01/2015 to 12/31/2019 and had a Respiratory Pathogen Array (RPA) sent within 48 hours of admission. Patients were identified using an automated query of the electronic medical records (epic clarity and enterprise explorer). Only the first admission of the patient was included in the study. Patients with pre-existing tracheostomy (ICD 10 code of Z 93.0) and patients with a diagnosis of chronic respiratory failure (ICD code J 96.1) were excluded. From this list of patients, we identified patients who had positive RPA. Patients positive for Bordetella pertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae on RPA were also excluded. Included patients were further categorized as patients who had only one virus identified, and patients who had more than one virus identified for descriptive and comparative analysis.

Children's Hospital of Illinois is a 138-bed hospital within the hospital system. It is the largest freestanding children's facility in downtown Illinois and comprise of representation of all pediatric subspecialties including pediatric congenital heart surgery. Pediatric critical care comprises of a 32-bed unit which includes 16 intermediate care beds. Intermediate care beds are "open" and hospital allows for direct admission to the intermediate care unit.

All the study variables were directly extracted by the automated query of the electronic medical records. This included demographics (age, weight, height, race, gender) as well as comorbidities. The comorbidities including the pre-existing diagnosis of prematurity (diagnostic code P07), asthma (diagnostic code J45), congenital heart disease (diagnostic code Q24), oncologic diagnosis (diagnostic code C1-C100) and developmental delay (diagnostic code R62.5) on any hospital encounter before the index encounter. Body Mass Index (BMI) was calculated based on the patient's weight, and height and all patients were characterized into BMI categories of underweight (< 18.5), normal (18.5 to 24.9), overweight (25 to 29.9) and obese (>=30). Age was also categorized as < one month, one month to 12 months, 12 months to 5 years and more than five years, and further as less than 12 months and more than 12 months for comparative analysis. Concurrent bacterial superinfection was assessed by the presence of positive culture (blood, respiratory, or urine) within 24 hours of hospital admission. Prescription of antibiotics (oral or intravenous) within six hours of admission was assessed based on electronic order start time within six hours of hospital admission time. The antibiotic duration was calculated as the difference in days between antibiotic ordered start time, and antibiotic ordered end time. We also identified patients who received antibiotics for more than five days. In this search, "antibiotic" was defined as a therapeutic class of "anti-infective" and antiviral agents like Tamiflu was included in the category. We also assessed patient management and resource utilization variables such as intermediate care unit admission, intensive care unit admission, intubation (placement of endotracheal tube during the encounter), chest x-ray, escalation of care (Transfer from lower acuity to a higher acuity unit) and total direct cost of care. Outcome variables included total ICU length of stay (total time in days spent in the ICU, if the patient was in ICU on two separate occasions during the hospital encounter, cumulative ICU days were calculated), hospital length of stay, ventilator duration (difference in days between endotracheal tube placement time and endotracheal tube removal time) and mortality (death date on the encounter).

All the variables were extracted in an excel file. The subtypes of viruses (Coronavirus 229E, HKU1, NL63, OC43, Influenza A, AH1, AH3, A2009H1, Influenza B, and Parainfluenza 1, 2, 3 and 4) were combined as Coronavirus, Influenza virus, and parainfluenza virus. Comparative analysis was then performed for patients who had single viral infection versus patients who had more than one virus infection. Patients with different strains of the single virus were counted as a single viral infection. The statistical analysis included a comparative analysis of the various demographic and outcome variables. We calculated the mean and standard deviation or median with an Interquartile Range (IQR) for continuous variables as appropriate, and proportions for categorical variables. Comparative analysis was performed by student t-test or Wilcoxon test for nonparametric data and chi-square test as appropriate. Outcome factors significant on univariate comparison were analyzed by multivariable regression after accounting for age (in months), comorbidities (prematurity, asthma, congenital heart disease, developmental delay and cancer) and bacterial coinfection is (blood, urine and respiratory). Length of stay and costs were log transformed and

parameters were exponentiated. Standard least square model was used for linear regression. P value of less than 0.05 was considered significant. All statistical analyses were performed using JMP version 12.4 (SAS Institute, Cary, NC).

Results

A total of 3699 patients had RPA sent within 48 hours of hospital admission in the study period (01/01/15 – 12/31/19). Among these patients, 2192 had a positive RPA and were included in the study. One thousand eight hundred thirty-one patients had only a single virus detected (Group A), while 361 had more than one virus detected (group B). Thirty-seven patients had three or more virus detected, four patients had four or more virus detected, and one patient had six viruses detected in the RPA.

A total of 2595 viruses were identified in the RPA of the included patients (including all the coinfections). Rhino enterovirus comprised almost half of all the viruses identified (n=1278, 49.2%). Proportion of other viruses included respiratory syncytial virus (n=422, 16.2%), parainfluenza virus (n=222, 8.5%), metapneumovirus (n=140, 5.3%), influenza virus (n=151, 5.8%), coronavirus (n=193, 7.4%), adenovirus (n=189, 7.2%). Among the patient with two virus coinfections, the most common combination was Rhino/enterovirus and respiratory syncytial virus (22.4%). The other common combinations were Rhino/enterovirus and adenovirus (17.4%), Rhino/enterovirus and parainfluenza virus (13.8%) and Rhino/enterovirus and coronavirus (8%). (Table 1).

The median age of the study population was 15.9 months (IQR 3.8, 43.8). Patients who had coinfection were significantly younger (11.3 [IQR 4.3, 25.1]) than patients hospitalized with single virus infection (17.0 [IQR 3.7, 48.8]), p= 0.001. There was a higher proportion of infants (50.9%) among patients who had coinfection, as compared to patients with single viral infection (41.3%), p <0.001. There was no difference in gender distribution or racial distribution in the two groups. Children with coinfection had an overall lower median weight; however, there was no significant difference in the body mass index or percentage of obese patients in the two groups. Overall positive urine culture was detected in 8.2% of total patients at the time of admission, while positive blood and respiratory culture were detected in 2.0% and 2.5%, respectively. A much higher proportion of patients with coinfection had a positive respiratory culture within 24 hours of hospital admission (4.7%) as compared to only 2.1% in patients with a single viral infection, p= 0.004. There was no significant difference in the patients who had positive blood culture or positive urine culture at the time of admission. Asthma was the most prevalent comorbidity and was present in 463 (21.1%) of the total patients. There was, however, no significant difference in the diagnosis of asthma between the two groups. Similarly, the two groups were similar in terms of the proportion of patients who were premature, had congenital heart disease, or had a pre-existing diagnosis of developmental delay. There was, however, a higher proportion of patients with single viral infection (4.0%) who had an oncologic diagnosis as compared to patients with coinfection and had an oncologic diagnosis (1.6%), p= 0.02. (Table No 2).

Overall, oral antibiotics were prescribed to 155 patients in the study population (7.0%), and intravenous antibiotics were prescribed to 646 patients (29.4%) within six hours of hospital admission. There was no difference in the proportion of patients who were prescribed oral or intravenous antibiotics among the two groups. The median intravenous antibiotic duration in the study population was one day (IQR 0, 2), and 24 patients (1%) received antibiotics that were prescribed at the time of admission, for five or more days. There was no difference between the two groups in terms of antibiotic duration. 60.7% of the patients received a chest x-ray (CXR) during the hospitalization. A higher proportion of patients with coinfection (66.4%) received CXR compared to patients with single virus infection (59.5%), p= 0.01. There was no difference in the number of chest x-rays performed during hospitalization in the two groups. Overall, 8.1% of the study population had a Pediatric Emergency Response Team (PERT) activation during the hospitalization, and this proportion was higher in patients with coinfection (11.6%) as compared to patients with single viral infection (7.4%), p= 0.007. Only six patients out of all included patients had “code blue” (cardiac arrest) during their hospitalization, and there was no difference in the two groups. The median cost of care for hospitalization of patients with viral -related illnesses was $ 2468.59 (IQR $ 1452.27, $ 4754.90). There was a significant difference in the two groups with a higher median cost of care ($ 2934.89) in patients with co-viral infections compared to patients with single viral infection ($ 2381.14), p= 0.002. (Table No 3). The difference in cost of care however did not persist on multi variable linear regression after accounting for confounders (parameter estimate 1.1104 coinfection versus single infection, P value 0.052) (data not shown)

Overall, 41.1% of the patients required intermediate level admission in the hospital, and 23.4% required ICU admission. There was no significant difference in the proportion of patients requiring intermediate or ICU admission among the two groups. Among the patient who required ICU admission, the median length of stay was 1.9 days (IQR 0.91, 4.76). There was no significant difference in the ICU length of stay between the two groups. A significantly higher proportion of patients with coinfection required initiation of high flow cannula (145/361, 40.1%) compared to patients with single viral infection (28.0%), p <0.001. This difference remained significant on multi variable logistic regression after accounting for confounders (p<0.001, data not shown). Similarly, a higher proportion of patients with coinfection (8.2%) required intubation compared to patients with single viral infection (5.6%); this difference, however, was not statistically significant, p= 0.07. The overall median duration of intubation for patients who required intubation was six days (IQR 2, 9). This was comparable in the two groups. The median hospital length of stay for the study population was two days (IQR 1, 4), and patients with coinfection stayed in the hospital for a significantly longer duration (3[IQR 1, 5] vs. 2 [IQR 1, 4], p= 0.0003). A total of seven patients died during hospitalization, with an overall mortality rate of 0.3%. There was no difference in mortality between the two groups. (Table No 4). The difference in hospital length of stay in the two groups were significant on multi variable linear regression with a parameter estimate of 1.116 for coinfection versus single infection, p=0.01 (data not shown).

Table 1: Prevalence of Viral illness and viral combinations in the study population.

Category	Virus/Combinations	N	Percent
Single virus	Rhino/enterovirus	1278	49.2%
	Respiratory syncytial virus	422	16.2%
	Parainfluenza virus	222	8.5%
	Meta Pneumovirus	140	5.3%
	Influenza virus	151	5.8%
	Coronavirus	193	7.4%
	Adenovirus	189	7.2%
Common Viral combinations	Rhino/enterovirus + respiratory syncytial virus	81	22.4%
	Rhino/entero virus+ Adenovirus	63	17.4%
	Rhino/entero virus + Parainfluenza virus	50	13.8%
	Rhino/enterovirus + Coronavirus	29	8%
	Respiratory syncytial virus + Coronavirus	29	8%
	Rhino/enterovirus + meta Pneumovirus	18	4.9%
	Adenovirus + Coronavirus	14	3.8%
	Respiratory syncytial virus + Adenovirus	13	3.6%
	Coronavirus + Influenza virus	10	2.7%
	Adenovirus + meta Pneumovirus	9	2.4%

Table 2: Demographic distribution of the study population.

		Cumulative (n= 2192)	Single virus infection (n= 1831)	Coinfection (n= 361)	P value
Age	Months	15.9 (3.8, 43.8)	17.0 (3.7, 48.8)	11.3 (4.3, 25.1)	0.0001W
Age distribution (% infants)		941 (42.9%)	757 (41.3%)	184 (50.9%)	0.0007C
Percent male		1248 (56.9%)	1031 (56.3%)	217 (60.1%)	0.18
Race	Caucasian	1510 (68.8%)	1271 (69.4%)	239 (66.2%)	0.48
	Black	498 (22.7%)	409 (22.3%)	89 (24.6%)	
	Other	184 (8.3%)	151 (8.2%)	33 (9.1%)	
Weight	Kilograms	10.2 (5.7, 15.8)	10.5 (5.6, 16.6)	9.1 (6.2, 12.1)	0.0004W
BMI		16.2 (14.7, 18.1)	16.2 (14.6, 18.1)	16.4 (14.8, 18.3)	0.26
Percent obese		37 (1.6%)	34 (1.86%)	3 (0.83%)	0.21
Bacterial coinfection	Positive blood culture	46 (2.0%)	38 (2.0%)	8 (2.2%)	0.86
	Positive respiratory culture	56 (2.5%)	39 (2.1%)	17 (4.7%)	0.004C
	Positive urine culture	180 (8.2%)	149 (8.1%)	31 (8.5%)	0.77
Comorbidity	pre-mature	277 (12.6%)	223 (12.1%)	54 (14.9%)	0.14
	Asthma	463 (21.1%)	399 (21.7%)	64 (17.7%)	0.08
	CHD	43 (1.9%)	39 (2.1%)	4 (1.1%)	0.20
	Developmental delay	131 (5.9%)	113 (6.1%)	18 (4.9%)	0.38
	Cancer	80 (3.6%)	74 (4.0%)	6 (1.6%)	0.02

Table 3: Resource utilization single versus coinfection.

	All sample	Single virus infection (n= 1831)	Coinfection (n= 361)	P value
Oral antibiotic	155 (7.0%)	125 (6.8%)	30 (8.3%)	0.31
Intravenous antibiotic	646 (29.4%)	542 (29.6%)	104 (28.8%)	0.76
IV antibiotic duration (Days, Median, IQR)	1 (0, 2)	1 (0, 2)	0 (0, 1)	0.28
IV antibiotics >5 days	24 (1.0%)	18 (0.98%)	6 (1.65%)	0.26
Chest x-ray	1331 (60.7%)	1091 (59.5%)	240 (66.4%)	0.01c
No of CXR, No (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.77
PERT	178 (8.1%)	136 (7.4%)	42 (11.6%)	0.007C
Code	6 (0.27%)	5 (0.27%)	1 (0.28%)	0.99
Direct cost Median (IQR)	$ 2468.59 ($ 1452.27, $ 4754.90)	$ 2381.14 ($ 1422.46, $ 4564.77)	$ 2934.89 ($ 1644.00, $ 5414.17)	0.002W

Table 4: Single versus coinfection outcome comparison.

		Cumulative (n= 2192)	Single virus infection (n= 1831)	Coinfection (n= 361)	P value
Intermediate admission	N (%)	901 (41.1%)	740 (40.4%)	161 (44.6%)	0.13[c]
ICU admission	N (%)	514 (23.4%)	419 (22.8%)	95 (26.3%)	0.15[c]
High flow nasal cannula	N (%)	658 (30.0%)	513 (28.0 %)	145 (40.1%)	<0.001[c]
Intubation	N (%)	134 (6.1%)	104 (5.6%)	30 (8.2%)	0.07[c]
Hospital length of stay (days)	Median (IQR)	2 (1, 4)	2 (1, 4)	3 (1, 5)	0.0003[w]
ICU length of stay (days)	Median (IQR)	1.9 (0.91, 4.76) (n= 514)	1.96 (0.91, 4.76) (n= 419)	2.18 (0.94, 5.13) (n= 95)	0.52[w]
Intubation duration (days)	Median (IQR)	6 (2, 9) (n= 126)	5 (2, 9) (n= 98)	6 (3, 10) (n= 28)	0.49[w]
Mortality	N (%)	7 (0.3%)	6 (0.3%)	1 (0.28%)	0.87[c]

Discussion

In this comprehensive cohort review, we have described the epidemiology, resource utilization, and outcomes of ALRI caused by one viral pathogen versus multiple viral pathogens in children requiring hospitalization. In our study, the overall mortality in children suffering from ALRI was low and showed no significant difference in the two groups, even with the inclusion of patients with comorbidities. However, patients with viral co-infections had a longer hospital stay, more utilization of high flow nasal cannula, higher possibility for escalated care and intubation, and increased cost of care.

Interestingly, rhino/enterovirus had the highest detection rate among children admitted with ALRI, accounting for 50% of all cases. This result differs from previous viral epidemiology studies [3], potentially because we only included patients that tested positive using respiratory pathogen array while patients tested with RSV antigen and rapid flu tests were excluded. RSV was the second most common isolated virus found in 16% of our population. Viral co-infections were reported in 16.2% of all cases admitted to our hospital with ALRI, which is relatively lower than the prevalence rates reported in previous studies [6,11,13,14]. These differences in viral co-detection rates might reflect variations in case selection and possible technical limitations. Even though COVID-19 was not isolated in our population and is known to vary genetically from the coronavirus identified in this study, it was reported that COVID-19 had the same pattern of co-infection with other respiratory viruses in the recent pandemic [15,16]. Data regarding COVID-19 is still evolving, but our results from this study might help in comparing outcomes of COVID-19 co-infection versus other viral co-infections in children. The higher proportion of infants among patients who had viral co-infections might be explained by the susceptibility of this age group to recurrent viral infections, immature immune response, higher rates of asymptomatic nasopharyngeal colonization, and prolonged shedding of rhino/enterovirus and RSV [17-23].

Patients with cancer were more likely to have one virus isolated rather than a combination of two or more viruses in our cases, which contrasts with prior studies that have shown a higher percentage of viral co-infections in pediatric patients with cancer and neutropenia [24,25].

Clinical course of patients with viral coinfection in our study was more severe, as depicted by the aforementioned variances (length of stay, high flow nasal cannula, intubation). Our contemporary data is similar to what has been reported in the literature [8-10].

A higher rate of patients with viral co-infection had a positive respiratory culture within 24 hours of hospital admission in comparison to patients with a single viral infection, which might be explained by the higher proportion of intubation in patients with viral co-infection, even though the difference was statistically not significant. Patients admitted with viral co-infections

were more likely to get chest x-rays. This might be attributed to the lower age group that was infected with multiple viruses and their relative severe clinical presentation.

Our study is the first to report the hospital cost of care for children with respiratory viral illnesses. Cost of care was high in patients with coinfections, even though the difference did not reach statistical significance. The overall cost of care to manage viral infection related admissions in children was low compared to other expenses in the healthcare industry.

Our study has several limitations. First, it was conducted retrospectively and from automated data extraction only which carries the possibility of incorrect charting. Also, identification of comorbidities was based on ICD codes entered by providers on admission. Second, the duration of viral shedding, as detected by RPA-PCR, is significantly longer than the culture of the same virus and could even reflect virus left over from a previous infection rather than a true active infection. Third, the significance of multiple viral detection remains poorly understood, given that PCR can sometimes detect a viral respiratory shedding in asymptomatic children [14,19]. Previous literature reported that hCoV and hBoV PCR were frequently detected in healthy controls, suggesting that caution is needed when inferring a causal relationship between viral detection and respiratory diseases in symptomatic and asymptomatic patients [26].

Conclusion

In conclusion, we have described the epidemiology of single respiratory viral illnesses versus multiple viral co-infections in children, including their comparative resource utilization and outcome. Appropriate identification of respiratory viruses can help us in isolating patients appropriately, as well as recognizing patients that might need escalated respiratory care, especially those with viral co-infections. Our study ended before the emerging COVID-19 was reported in the United States. However, the data can help us understand the disease course of COVID-19 and the role of viral co-infections in altering the inflammatory response in the pediatric population.

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