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Clinical Characterization of Children Presenting to the Hospital with Enterovirus D68 Infection During the 2014 Outbreak in St. Louis

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Abstract

Background—The largest known outbreak of enterovirus D68 (EV-D68) infections occurred during 2014. The goal of our study is to characterize the illness severity and clinical presentation of children infected with enterovirus-D68 (EV-D68) in comparison to non-EV-D68-Human Rhino/Enteroviruses (HR/EV).

Method—Our study is a retrospective analysis of severity level, charges and length of stay of children who presented to St. Louis Children's Hospital from 8/31/2014–10/31/2014 and tested positive for EV-D68 in comparison to non-EV-D68-HR/EV infected patients. Chart review was performed for all EV-D68 infected patients and age and severity matched non-EV-D68-HR/EV infected patients.

Result—There was a striking increase in hospital census in August of 2014 in our hospital with simultaneous increase in the number of patients with EV-D68 infection. There was no significant difference in severity of illness, length of stay or total charges between EV-D68 and non-EV-D68-HR/EV infected children. EV-D68 infection was characterized by presenting complaints of difficulty breathing (80%) and wheezing (67%), and by findings of tachypnea (65%), wheezing (71%) and retractions (65%) on examination. The most common interventions were albuterol (79%) and corticosteroid (68%) treatments and the most common discharge diagnosis was asthma exacerbation (55%).

Conclusion—EV-D68 caused a significant outbreak in 2014 with increased hospital admissions and associated increased charges. There was no significant difference in severity of illness caused by EV-D68 and non-EV-D68-HR/EV infections suggesting that the impact from EV-D68 was due to increased number of infected children presenting to the hospital and not necessarily due to increased severity of illness.

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Keywords

Enterovirus D68; Human rhino/entero virus; Acute Flaccid Myelitis

Introduction

Enterovirus D68 (EV-D68) was first isolated in 1962 from the throat swabs of four children with acute lower respiratory tract illness.¹ Only 26 cases were reported in the United States between 1970 and 2005.^{2,3} From 2008–2010 small outbreaks (11–39 cases) were reported in Asia, Europe and the U.S., with the majority of cases occurring in children.⁴ An unusually large outbreak of EV-D68 disease was noted in the United States in August 2014, initially in the midwestern states, then spreading across the country and appearing in other parts of the world.^{2,5–14} The Centers for Disease Control and Prevention reported 1153 patients positive for EV-D68 in the United States as of March 23, 2015.¹⁵

We observed an increase in the number of children presenting to our institution with respiratory infections in August 2014, which we suspected were due to EV-D68 infections. We sought to characterize this outbreak after developing a highly specific and sensitive reverse transcriptase polymerase chain reaction (RT-PCR) assay that was used to confirm EV-D68 in nasopharyngeal specimens of children who were positive for Human Rhinoviruses or Enteroviruses (HR/EV).¹⁶ The goal of the present study was to: 1) compare the 2013 and 2014 summer/fall HR/EV seasons to determine the impact of 2014 EV-D68 disease outbreak on our hospital, intensive care unit (ICU) and emergency department (ED) census; 2) to compare the severity of illness (defined by ICU admission), length of stay, and charges incurred by children infected with EV-D68 to children infected with non-EV-D68-HR/EV; and 3) to describe the presenting symptoms, physical findings, and hospital course of children with EV-D68 infections in comparison to those with non-EV-D68-HR/EV infections.

Methods

Study setting

Our study site was St. Louis Children's Hospital (SLCH) a university-affiliated, tertiary care children's hospital with 264 beds, 10,542 admissions per year and over 48,966 emergency visits per year.

Census data

We obtained census data on all patients admitted to the hospital (excluding the neonatal intensive care unit), ICU, and the ED at SLCH from 07/01 to 10/31 of 2013 and 2014. Census data was obtained from SLCH Hospital Health Information Management System (HIMS), an administrative database that is updated daily with patient demographics, charges and payments from the hospital's financial system, admitting system and electronic health records.

Virologic testing

Data on all children presenting to SLCH who were positive for HR/EV by multiplex PCR on the FilmArray Respiratory Panel (BioFire, Salt Lake City) during the study period was obtained from the Diagnostic Virology Laboratory data base. The FilmArray panel does not differentiate between rhinoviruses and enteroviruses (reported as HR/EV) but does detect EV-D68.¹⁶ In general, physicians at our institution test nasopharyngeal specimens by multiplex assay in children with respiratory or other systemic symptoms and are likely to be admitted. In addition, testing is performed on children presenting to the ED with respiratory or other systemic symptoms at the discretion of the evaluating physician. Specimens were collected by flocked Dacron swabs and stored in Universal Viral Transport Media until testing.

Specimens from children at SLCH that tested positive for HR/EV were subsequently tested with an EV-D68 specific RT-PCR assay (Wash U Design 1).¹⁶ Selected HR/EV-positive specimens that tested negative for EV-D68 by RT-PCR were typed by PCR-sequencing to determine circulating HR/EV types in addition to EV-D68.¹⁷ Specimens selected for typing were weighted towards severe cases.

The SLCH Diagnostic Virology Laboratory also receives nasopharyngeal specimens for multiplex testing from 11 additional hospitals caring for adults in the Barnes Jewish Hospital Healthcare system (which covers the mid-Missouri and southern Illinois regions). Of 354 HR/EV-positive tests in patients 19 years of age, there were 157 specimens that were available for testing for EV-D68.

Analysis of illness severity

All children (< 19 years old) who were evaluated in the SLCH ED and/or were admitted to the hospital from 8/01/2014–10/31/2014, and whose nasopharyngeal specimens were positive for HR/EV and tested for EV-D68 (as described in the previous section) were included in this analysis. Only the first visit for each patient to SLCH was included to ensure that each patient was only represented once. We excluded patients in the neonatal intensive care unit, those seen only in outpatient clinics, as well as those whose first nasopharyngeal specimen positive for HR/EV was obtained >72 hours after admission.

For patients that met the above criteria we compared disease severity, length of stay, discharge diagnosis, and charges incurred. Illness severity was defined as: mild (discharged from the emergency department/outpatient clinic); moderate (admitted but not treated in an intensive care unit (ICU)); or severe (admitted to the ICU at any time). Patient demographics, discharge diagnosis, and charge data was obtained from the SLCH health information system. Length of stay (LOS) and severity level (mild, moderate and severe data) was obtained from the electronic health record clinical database.

Chart review of EV-D68-positive and severity and age matched non-EV-D68-HR/EV patients

Patients were excluded after chart review if: 1) they were admitted for elective procedures or trauma with no respiratory symptoms; 2) they were still hospitalized when collection of study data commenced; or 3) they were not evaluated by a hospital staff physician or

advanced nurse practitioner (e.g., if they were sent by a community physician to the outpatient lab for testing). Patients seen in outpatient clinic were included for chart review analysis.

History of presenting illness, past medical history, medications at time of admission, physical examination findings, interventions received in the hospital, and discharge diagnoses was obtained by chart review. Chart reviews were performed by four study physicians blinded to the EV-D68 status of the patient. Study data were collected and managed using REDCap (Research Electronic Data Capture), which is a secure web-based data capture application hosted at Washington University in St. Louis.¹⁸ One author audited 10% of all charts reviewed to ensure accuracy in data collection. Comparison of 33 chart reviews showed an overall inter-reviewer concordance of 96% across all parameters of the instrument.

This study was approved by the Washington University Human Research Protection Office.

Statistical analysis

Categorical variables were analyzed with Pearson chi-square tests of independence or Fisher's Exact tests. Continuous variables were analyzed with Wilcoxon rank-sum tests except that length of stay was analyzed with an independent-sample t-test after log base 10 transformation. For the matched pair analysis, categorical variables were analyzed with McNemar's tests for paired data. Variables were grouped into families having a logical relationship, such as history of present illness, past medical history, and types of intervention, and adjustment for multiple testing was applied using the step-down Bonferroni method within the SAS/Stat MULTTEST procedure. Subgroup analysis between EV-D68-positive and non-EV-D68-HR/EV children with no underlying disease other than wheezing was performed by Pearson chi-square or Fisher's exact test for categorical variables and Wilcoxon Rank Sum for continuous variables. All analyses were done with SAS/Stat software Version 9.3 of the SAS System for Windows (Copyright 2010 SAS Institute Inc).

Results

Virologic testing

There were 597 HR/EV-positive specimens from 8/31/2014 to 10/31/2014, a period during which laboratory personnel were requested to save such specimens. Of these, 513 (86%) were available for further testing by EV-D68 RT-PCR, as laboratory personnel were not able to save all specimens. One hundred and forty-five (28%) of those specimens tested positive for EV-D68, and patients providing those specimens comprised the bulk of the EV-D68 study group. There were 21 additional archived HR/EV-positive samples from 08/01/2014–08/30/2014, (a period when all HR/EV specimens were not yet being routinely saved) that were available for EV-D68 testing. Of these, 9 (43%) tested positive for EV-D68. Thus, a total of 154 EV-D68-positive patients were included in the study. There were 380 non-EV-D68-HR/EV patients during this time period. After excluding patients who met exclusion criteria, 467 patients (147 EV-D68-positive and 320 non-EV-D68-HR/EV patients) were

included in the analysis for comparison of severity level, LOS and charges between the two groups.

For chart review, each of the 154 EV-D68-positive patients was matched first by severity level and then by age in months to a patient who was infected with non-EV-D68-HR/EV. Based on information from the chart review of those 308 patients, exclusion criteria as described in the method section were applied to generate the 139 matched pairs for analysis. In addition to pediatric patients treated at SLCH, 157 HR/EV-positive referral specimens for patients 19 years of age were tested, and 18% of these were positive for EV-D68.

Impact of patients with EV-D68 infection on hospital census

Compared to the same period in 2013, we observed a striking increase in the number of HR/EV-positive patients beginning in August, 2014, peaking around August 31 (Figure 1A), as well as an increase in the number of hospital admissions. The peak in admissions overlapped directly with the peak in HR/EV-positive infections (Figure 1B). Admissions to the ICU's and ED visits in August 2014 were also notably increased (Figure 1B). Analysis of EV-D68 testing by week revealed that 64% of specimens tested were positive during the period of peak HR/EV activity in late August, 2014 (Figure 1A). None of the archived specimens from 2013 were positive for EV-D68 (data not shown). Of 126 patients tested after Oct 21, 2014 none were EV-D68-positive (data not shown).

Analysis of illness severity in children infected with EV-D68 compared to non-EV-D68-HR/EV infected children (unmatched population)

Analysis of demographics revealed no differences in gender or ethnicity between EV-D68 infected and non-EV-D68-HR/EV infected patients (Table 1). The median age of children infected with EV-D68 was higher than the non-EV-D68-HR/EV infected children. The majority of both EV-D68-positive and non-EV-D68-HR/EV children had moderate illness (Table 1). Less than 20% of children in both groups had severe illness, and there was no significant difference in disease severity level between the two groups. In addition, there was no significant difference in total or ICU LOS between the two groups of children. There was no significant difference in the total charges incurred by EV-D68-positive or negative children. However, EV-D68-positive children had higher respiratory charges and lower laboratory charges compared to non-EV-D68-HR/EV infected children (Table 1).

We sought to determine if a more severe predominant non-EV-D68-HR/EV type was circulating during the 2014 outbreak that could account for a significant proportion of severe disease in the non-EV-D68-HR/EV group. As shown in Table 2, there was no predominant non-EV-D68-HR/EV type in any severity group in children tested, with representation from A, B, and C HRV species. Importantly, all of these specimens that tested as non-EV-D68 by RT-PCR were also non-EV-D68 by sequencing, reflecting the high specificity of the EV-D68 RT-PCR test that has been previously demonstrated.¹⁶

Presenting history, physical examination findings and hospital course of EV-D68-positive children

In order to characterize the clinical presentation of disease caused by EV-D68 infection, we reviewed charts of patients infected by EV-D68 and compared them with severity- and age-matched non-EV-D68-HR/EV patients. The mean age of patients in the matched cohort was 5.3 years, the majority (91%) were inpatients, and 18% were admitted to the ICU. The median day of presentation to the hospital was at day 3 of illness (IQR 2–4) based on histories reported by caregivers.

Almost all children infected with EV-D68 (96%) presented with symptoms of upper respiratory tract infection (URI): cough, rhinorrhea, and/or sore throat (Table 3). Noteworthy was the high prevalence in the history of present illness of difficulty breathing (80%) and wheezing (67%), and findings of tachypnea (65%), wheezing (71%) and retractions (65%) on examination (Table 3). The majority of EV-D68 infected children (75%) had no history of underlying disease other than wheezing, but 63% had a past medical history of wheezing and 52% reported use of albuterol at the time of admission. The most common interventions received by EV-D68 infected children in the hospital were albuterol treatments (79%) and corticosteroids (68%), and the most common discharge diagnosis was asthma exacerbation (55%) (Table 4). There were no deaths or cases of acute flaccid myelitis (AFM) among EV-D68-infected children.

Comparison between EV-D68-positive versus severity and age matched non-EV-D68-HR/EV infected children

We performed a matched pair analysis to identify features that distinguished patients with EV-D68 infections from non-EV-D68-HR/EV infections. Two principle findings were evident from the clinical presentation and hospital course (Tables 3 and 4). First, a significantly greater proportion of EV-D68-positive patients had symptoms of wheezing at presentation (67% vs. 44%, $p=0.004$), had wheezing on examination at presentation (71% vs. 55%, $p=0.05$), and received treatment with IV magnesium sulfate (16% vs. 6%, $p=0.02$) compared to non-EV-D68-HR/EV infected children. Second, a significantly smaller proportion of EV-D68-positive patients had a history of underlying diseases other than wheezing compared to non-EV-D68-HR/EV patients. This was evident from a number of findings in EV-D68-positive compared to non-EV-D68-HR/EV patients: 1) fewer reported a history of underlying disease other than wheezing (25% vs. 40%, $p=0.03$); 2) fewer reported taking antibiotics at time of admission (3% vs. 12%, $p=0.03$); 3) fewer received antibiotics in the hospital (15% vs. 32%, $p=0.006$); 4) fewer received other interventions such as an operative procedure or placement of peripherally inserted central catheter in hospital (6% vs. 18%, $p=0.005$); 5) fewer had been hospitalized in the past year (16% vs. 29%, $p=0.03$); and 6) fewer had a discharge diagnosis of an infectious disease such cellulitis, bacteremia, or urinary tract infection (5% vs. 15%, $p=0.02$).

Comparison of children with no underlying disease other than wheezing among EV-D68-positive and non-EV-D68-HR/EV infected patients

Due to the finding that a large proportion of non-EV-D68-HR/EV controls (40%) had a history of underlying disease other than wheezing, comparisons between the two groups

may have been confounded by underlying disease present in the matched control population. We therefore analyzed the two groups after excluding all patients with underlying disease (other than wheezing) (EV-D68-positive cases N=109, non-EV-D68-HR/EV controls N=88). There were no significant differences in gender, ethnicity, insurance status, history at presentation, physical examination at presentation, use of antibiotics at time admission, past medical history of wheezing, history of hospitalization in the past year, interventions received, or discharge diagnoses between the two groups of children (data not shown). In addition, there was no significant difference in LOS or total, respiratory, laboratory, pharmacy, or other charges between the two sub groups (supplemental Table 1).

Discussion

Our study analyzed the outbreak of EV-D68 disease in 2014, providing a detailed characterization of the impact of this outbreak on hospital resources and the severity of illness caused by this virus at a single Midwestern U.S. tertiary care center. There was a significant increase in hospital, ED, and ICU census in the fall of 2014 in our hospital with a simultaneous increase in patients positive for HR/EV. EV-D68 activity was highest during this period leading to the conclusion that the outbreak of EV-D68 infections was the cause for the increased census in the hospital.

There was no significant difference in severity of illness caused by EV-D68 infection compared to that caused by non-EV-D68-HR/EV. In addition, there was no significant difference in the length of stay or total charges between the two groups of children. Our findings are consistent with a recent study from Alberta, Canada which found no difference in disease severity as defined by ICU admission in 49 EV-D68-positive children in comparison to children with non-D68 enterovirus infections.⁷ Our rates of patients with severe disease (18%) as defined by ICU admissions is similar to that seen in study by Schuster et al. at their institution.¹² Although we found no difference in disease severity between EV-D68 and non-EV-D68-HR/EV infected patients, 18% of EV-D68 patients were admitted to the ICU, underscoring that HR/EV infections can result in severe disease.

EV-D68-positive children in our study presented most commonly with signs and symptoms of URI-associated reactive airway disease, including rhinorrhea, cough, wheezing, and difficulty breathing. These findings are consistent with early reports at the onset of the EV-D68 outbreak from Kansas City (N=19) and Chicago (N=11).⁵ Sixty-eight percent of children in the Kansas City outbreak had a history of asthma or wheezing and all patients had difficulty breathing and hypoxemia, whereas 73% of patients from Chicago had a history of asthma or wheezing.⁵ In our study, 63% of EV-D68-positive children had a past history of wheezing, and the primary intervention received by EV-D68-positive children was albuterol treatments and steroids. Thus, we can conclude that EV-D68 primarily causes respiratory illness associated with wheezing in children with a history of wheezing.

An important finding in our study was that fewer EV-D68-positive patients had underlying disease other than wheezing compared to non-EV-D68-HR/EV children. 75% of EV-D68 positive children had no history of underlying disease (other than wheezing) compared to 60% of non-EV-D68-HR/EV infected children. Other indicators of co-morbidities (such as

antibiotic use at time of admission, history of hospitalization in the previous year) were less frequently observed in EV-D68-positive patients. Nevertheless, no significant differences were found in the LOS between the two groups of children, thereby suggesting that their overall clinical course was not significantly different. Thus, although a significant number of children with EV-D68 infections had a history of wheezing, they had significantly less other co morbidities compared to children with non-EV-D68-HR/EV infections.

We also analyzed the subgroups of children with no underlying disease other than wheezing to remove the confounding effects of chronic diseases (other than wheezing). Our subgroup analysis showed that there is no significant difference in clinical presentation of children infected with EV-D68 in comparison to non-EV-D68-HR/EV in the subgroups with no underlying disease other than wheezing.

Our study provides valuable information on the cost of the EV-D68 outbreak for our hospital, which may be useful for health care planning for future outbreaks. There was no significant difference in total charges incurred by EV-D68-positive patients compared to non-EV-D68-HR/EV infected patients. In addition, the LOS between the two groups was not significantly different. There was a significant increase in our hospital census during the study period attributable to the outbreak of EV-D68 infections. This suggests that the increased burden on hospital resources from EV-D68-positive patients resulted from an increased census due to the outbreak rather than increased charges per patient compared to non-EV-D68-HR/EV infected patients.

Although there is increasing evidence linking EV-D68 infection with acute flaccid myelitis (AFM), no patients in our chart review cohort were found to have AFM.^{19–21} Sequencing and phylogenetic analysis of the genomes of AFM-associated EV-D68 viruses in another study show that they belong to clade B1 with multiple polymorphisms that are also found in other neurovirulent enteroviruses such as EV-70 and poliovirus.¹⁹ The genome sequence of EV-D68 circulating in St. Louis during the outbreak shared these polymorphisms.²² However, not all children infected with viruses containing these polymorphisms develop AFM.¹⁹ Therefore, additional host specific factors may underlie susceptibility to neurological symptoms associated with EV-D68, as has been suggested.¹⁹

There are some limitations to our study. This study is a description of EV-D68 disease in a case series of children at a single site. Our institution is a tertiary care center with a medically complex population, and as such, the presentation and scope of infection may differ from children at other institutions. However, we did characterize disease in a diverse set of patients consisting of previously healthy and medically complex children suggesting that our findings are generally relevant to children hospitalized with EV-D68 infection. Our inclusion criteria were limited to children presenting to our hospital/emergency department or outpatient clinic. Therefore, our study population has a strong selection bias towards children requiring a visit/ admission to the hospital. Our study population is also biased towards children who were tested due to respiratory or other systemic symptom and/or were likely to be admitted to the hospital. However, the strength of this study is that our study population included all children presenting to our institution who tested positive for EV-D68 with no selection of patients with severe disease. In addition, the EV-D68 specific RT-PCR

assay used in our study is 100-fold more sensitive than the published CDC assay, with an analytic limit of detection of 4 copies per reaction.

In conclusion, EV-D68 caused a significant outbreak in 2014 with increased hospital admissions and associated increased charges. EV-D68 primarily causes respiratory illness associated with wheezing. There was no significant difference in severity of illness caused by EV-D68 compared to non-EV-D68-HR/EV infections suggesting that the impact from EV-D68 was due to increased number of infected children presenting to the hospital and not necessarily due to increased severity of illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Human rhino/enterovirus testing, enterovirus D68 testing, and hospital census at SLCH. Note difference in scale of left and right Y-axes in (A), and different scales of left axes in each panel of (B). Bars in (A) represent total number of HRV/EV-positive specimens tested, with shaded portion representing those positive for EV-D68. *, EV-D68 RT-PCR data in (A) for weeks from 7/29/14 through 8/24/14 is a convenience sampling of a smaller number of archived specimens (see text for details).

Table 1

Comparison of demographic characteristics, severity levels, LOS, discharge diagnosis and charges for EV-D68-positive and non-EV-D68-HR/EV patients

	EV-D68-positive	non-EV-D68-HR/EV	
	Number (%)		p-value
Total patients	147 (31)	320 (69)	
Gender			
Female	65 (44)	125 (39)	0.29
Race			
African American	86 (59)	155 (48)	
Caucasian	52 (35)	148 (46)	0.14
Other	9 (6)	17 (6)	
Median age years (IQR)	4 (2–9)	2 (1–7)	0.004
Severity Level			
Mild	13 (9)	29 (9)	
Moderate	106 (72)	235 (73)	0.92
Severe	28 (19)	56 (18)	
Expired	0	2 (1)	
Discharge Diagnosis			
Respiratory Illness	121 (82)	222 (69)	0.003
Non-respiratory illness	26 (18)	98 (31)	
Length of stay, Median (IQR)			
Total days	1.7 (1–2.7)	1.6 (0.9–2.8)	0.27
Moderate total days ^a	1.4 (0.8–2.0)	1.4 (0.9–2.2)	0.83
Severe total days ^b	3.7 (2–6.1)	4.9 (2.4–11.5)	0.14
ICU days	1.7 (0.9–2.7)	1.8 (0.8–6.8)	0.34
Charges Median (IQR) \$\$			
Total	6529 (4559–10,809)	7040 (4598–13,062)	0.29
Respiratory	900 (240–1763)	600 (0–1439)	0.003
Laboratory	662 (662–1133)	900 (662–2516)	<0.0001
Pharmacy	439 (208–1174)	475 (182–1383)	0.86
Other	3842 (2666–7957)	4132 (2676–8083)	0.1

^aRefers to total LOS for patients with moderate severity (admitted with no ICU stay)

^bRefers to total LOS for patients with severe illness (had ICU stay during hospitalization)

Table 2

Typing results for a selection of non-EV-D68-HR/EV specimens

Severity	Patient #	Species	Type
Mild	1	HRV-B	R83
	2	HRV-A	W28
Moderate	3		W24
	4	HRV-C	W29
	5		W31
	6		R30
	7	HRV-A	R47
	8		R49
	9		R81
	10	HRV-B	R48
	11		R48
	12		W8
	13		W8
Severe	14		W11
	15	HRV-C	W17
	16		W24
	17		W27
	18		W27
	19		W31

Table 3

Comparison of findings at presentation between EV-D68-positive and non-EV-D68-HR/EV patients matched by age and severity levels.

	EV-D68- positive (n=139)	Non-EV- D68- HR/EV (n=139)		
	Number (%)		p-value	Adjusted p value*
History of present illness				
Fever	66 (48)	61 (44)	0.49	> 0.99
Upper respiratory tract symptoms ^a	133 (96)	122 (88)	0.01	0.07
Difficulty breathing	110 (80)	93 (67)	0.02	0.08
Wheezing	92 (67)	61 (44)	< 0.001	0.004
Vomiting, diarrhea, or abdominal pain	51 (37)	51 (37)	> 0.99	> 0.99
Decreased oral intake and/or decreased urine output	56 (40)	49 (35)	0.41	> 0.99
Other presenting complaints ^d	28 (20)	46 (33)	0.01	0.07
Medications at time of admission				
Corticosteroids	21 (51)	18 (13)	0.61	> 0.99
Antibiotics	4 (3)	16 (12)	0.007	0.03
Albuterol	72 (52)	60 (43)	0.15	0.45
Other medications	26 (19)	35 (25)	0.15	0.45
Past medical history				
Wheezing	88 (63)	74 (53)	0.07	0.14
History of any underlying disease (other than wheezing) ^c	35 (25)	55 (40)	0.01	0.03
Hospitalization in past year	22 (16)	40 (29)	0.01	0.03
Physical examination				
Fever (Temp $\geq$ 38.0)	13 (9)	22 (16)	0.13	> 0.99
Rhinorrhea	34 (24)	38 (27)	0.59	> 0.99
Rash	11 (8)	11 (8)	> 0.99	> 0.99
Tachypnea	91 (65)	82 (59)	0.23	> 0.99
Wheezing	99 (71)	76 (55)	0.004	0.05
Retractions/flaring/grunting/head bobbing/abdominal breathing	92 (65)	84 (60)	0.24	> 0.99
Other respiratory exam abnormality ^b	12 (11)	26 (25)	0.02	0.22
Tachycardia	59 (42)	70 (50)	0.16	> 0.99
Delayed capillary refill (CR > 3 sec)	4 (3)	6 (4)	0.53	> 0.99
Abnormal abdominal examination	6 (4)	14 (10)	0.05	0.41
Abnormal neurological examination	4 (3)	5 (4)	0.74	> 0.99

^aUpper respiratory tract symptoms included rhinorrhea, cough and sore throat.

^bOther respiratory abnormalities included findings such as stridor, decreased aeration, and coarse breath sounds.

^cHistory of underlying disease other than wheezing includes chronic non asthma respiratory disease, cardiac, hematological, oncological, neurological, endocrine, renal, metabolic, genetic or other diseases.

^dOther presenting complaints are those complaints not listed in the table such as headache, chest pain, cellulitis, etc.

* p-values which were adjusted for multiple comparisons by step down Bonferroni.

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Table 4

Interventions received in the hospital and discharge diagnosis of EV-D68-positive and non-EV-D68-HR/EV patients matched by age and severity levels

	EV-D68-positive (n=139)	EV-D68-negative (n=139)		
	Number (%)		p-value	Adjusted p value [*]
Interventions Received				
Oxygen by nasal cannula or face mask	36 (26)	25 (18)	0.08	0.56
Intravenous fluids	56 (40)	60 (43)	0.59	> 0.99
Albuterol treatment	110 (79)	93 (67)	0.02	0.16
Intravenous or oral antibiotics	21 (15)	45 (32)	< 0.001	0.006
Intravenous or oral steroids	94 (68)	80 (58)	0.08	0.56
Intravenous magnesium sulfate	22 (16)	8 (6)	0.002	0.02
Other interventions ^a	8 (6)	25 (18)	< 0.001	0.005
Noninvasive ventilation	11 (8)	6 (4)	0.13	0.65
Intubated	2 (1)	4 (3)	0.32	> 0.99
Continuous albuterol	13 (9)	7 (5)	0.03	0.27
Other interventions in ICU	2 (1)	3 (2)	0.56	> 0.99
Discharge Diagnosis				
Asthma exacerbation	76 (55)	56 (40)	0.01	0.05
Bronchiolitis	13 (9)	9 (6)	0.34	0.66
First time wheezing or viral induced wheezing	14 (10)	6 (4)	0.07	0.28
Other respiratory diseases	15 (11)	21 (15)	0.29	0.66
Infectious Disease ^b	7 (5)	21 (15)	0.003	0.02
Other discharge diagnoses	16 (12)	23 (16)	0.22	0.66

^a Includes other interventions such as seizures treated with antiepileptic, any operative procedure, placement of peripherally inserted central catheter etc.

^b Discharge diagnosis of infectious disease encompasses a wide variety of diagnosis such as cellulitis, bacteremia, croup, urinary tract infection etc.

ICU: Intensive care unit.

^{*} Indicates p-values which were adjusted for multiple comparisons by step down Bonferroni.