Published in final edited form as:

Pediatr Pulmonol. 2017 June ; 52(6): 827–832. doi:10.1002/ppul.23661.

A Comparison of Hospitalized Children with Enterovirus D68 to those with Rhinovirus

Charles B. Foster, MD¹, Ritika Coelho, MD¹, Paul M. Brown, PhD², Aman Wadhwa, MD¹, Amena Dossul, MD¹, Blanca E. Gonzalez, MD¹, Silvia Cardenas, MD³, Camille Sabella, MD¹, Debbie Kohn⁴, Sherilynn Vogel⁴, Belinda Yen-Lieberman, PhD^{2,4}, and Giovanni Piedimonte, MD^{2,3}

¹Center for Pediatric Infectious Diseases, Cleveland Clinic Children's, Cleveland, OH 44195

²Center for Pediatric Research, Cleveland Clinic Children's, Cleveland, OH 44195

³Center for Pediatric Pulmonary Medicine, Cleveland Clinic Children's, Cleveland, OH 44195

⁴Department of Laboratory Medicine, Cleveland Clinic, Cleveland, OH 44195

Abstract

Background—During the Fall of 2014, numerous children were hospitalized with asthma or respiratory distress related to Enterovirus D68 (EV-D68). A large proportion initially tested positive for rhinovirus. During this period our laboratory noted a cross-reactivity between EV-D68 and the rhinovirus component of the GenMark multiplex respiratory viral panel. Many other laboratories used assays not designed to distinguish these *Picornoviridae*.

Methods—To compare the presentation and outcomes of patients with rhinovirus and EV-D68, 103 GenMark rhinovirus positive nasopharyngeal swabs from hospitalized children were retested for EV-D68.

Results—EV-D68 positive patients vs EV-D68 negative patients were more likely to have a history of asthma (33.3% vs 11.0%, $P = 0.02$) and to present with acute respiratory illness (66.7% vs 40.2%, $P = 0.048$), especially status asthmaticus (47.6% vs 2.4%, $P < 0.001$). On admission they had more wheezing, respiratory distress, and lower respiratory tract involvement, and were more likely to be treated with steroids and discharged home on asthma medications. Respiratory viral coinfection was less common in EV-D68 positive vs EV-D68 negative patients. In patients without a respiratory viral coinfection the overall findings were similar.

Conclusion—Patients with EV-D68 vs rhinovirus were more likely to have a history of asthma, to present with status asthmaticus, to wheeze on admission, and to receive treatment with asthma medications in hospital and at discharge. The inability of common assays to distinguish EV-D68 from rhinoviruses raises the possibility that the role of EV-D68 as a viral trigger of asthma has been under appreciated.

Keywords

Enterovirus D68; rhinovirus; asthma; children; respiratory virus

Introduction

In the Fall of 2014, numerous children were hospitalized in the United States with severe lower respiratory symptoms and asthma. A large proportion of these tested positive for rhinovirus^{1,2}. During this period our laboratory, and others, noted a previously undocumented cross-reactivity between EV-D68 and the rhinovirus component of the GenMark multiplex respiratory viral panel³. In addition, the real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assays that are used by many hospitals to detect rhinovirus or enterovirus are not designed to distinguish between these closely related *Picornaviridae*. In this study, we screened a collection of GenMark rhinovirus positive nasopharyngeal swabs for EV-D68 using a specific rRT-PCR assay and investigated the clinical outcomes of children positive for rhinovirus compared to EV-D68.

Respiratory viruses are detected in up to 85% of children with asthma exacerbations, and rhinoviruses account for approximately two-thirds⁴. Infants who develop virus-induced wheezing may be at increased risk for subsequent asthma, and once asthma has established rhinoviruses may be the most common trigger of acute exacerbations. Human rhinoviruses are diverse and the epidemiology is complex, with over 150 distinct strains divided in to three major groups A, B and C⁴.

The inability of common assays to distinguish EV-D68 from rhinoviruses raises the possibility that the role of EV-D68 as a viral trigger of asthma has been under appreciated. Moreover, with the abrupt emergence in the Fall of 2014 of epidemic asthma associated with EV-D68, questions were raised as to whether EV-D68 might contribute to the well-documented seasonal surge in asthma admissions².

Using banked samples collected over a 16 month period from hospitalized children who underwent multiplex respiratory viral testing, we compared the clinical manifestations and discharge outcomes of patients who tested positive for EV-D68 to those who tested positive for rhinovirus.

METHODS

A retrospective chart review was performed on 103 pediatric patients (age < 18 years) admitted to Cleveland Clinic Children's main hospital between December 2013 and March 2015 who underwent multiplex respiratory viral testing (eSensor®, GenMark Diagnostics) during their admission and tested positive for rhinovirus. The multiplex assay screens for the following respiratory viruses: influenza (A, A H1, A H3, A 2009 H1N1, and B), respiratory syncytial virus (A and B), parainfluenza virus (1, 2, and 3), human metapneumovirus, human rhinovirus, and adenovirus (B/E and C). Children admitted to our inpatient units routinely undergo respiratory viral testing for diagnostic or epidemiologic management if they present with or develop respiratory symptoms suggestive of a viral respiratory

infection. The population included both children who presented primarily for respiratory symptoms and children in hospital for non-respiratory illnesses, such as cancer or organ transplant, who developed respiratory symptoms. The decision to perform respiratory testing was made by the clinical care team. Approval for the study and to perform additional testing for EV-D68 on banked residual specimen was provided by the Cleveland Clinic's Institutional Review Board.

Available, banked residual nasopharyngeal swab samples were tested in a blinded manner for EV-D68 on a BioRad CFX thermal cycler using a highly EV-D68 specific rRT-PCR primer set developed by Wylie *et al*⁶. RNA-extraction was performed using the QIAmp Viral RNA Mini kit on a QiaCube automated nucleic acid extractor (QIAGEN, Valencia, CA). Positive controls for EV-D68 (VR-1197) and human rhinovirus 1B (VR-1645) were purchased from American Type Culture Collection (ATCC, Manassas, VA) and were extracted from *in vitro* H1-HeLa cell (CRL-1958, ATCC) cultures.

The EV-D68 assay established in our laboratory was validated by sending 31 samples to the CDC for EV-D68 testing by their rRT-PCR assay and for direct sequencing of the enterovirus VP1 gene⁵. The samples sent to the CDC included 25 that had tested positive in our laboratory for EV-D68 and 6 that had tested negative. In total, 10 of the EV-D68 positive samples sent to the CDC for validation were from patients included in this study. The 21 additional samples did not meet this study's inclusion criteria because they were obtained on non-pediatric or non-hospitalized patients or the GenMark multiplex RVP was not performed. Four samples from this study were tested by the Ohio Department of Health using the CDC's rRT-PCR assay.

The chart review was performed by physicians blinded to EV-D68 test results. History of asthma or wheezing was obtained through review of past medical history as documented in admission and discharge notes, and was considered positive if there was a stated history of asthma, wheezing or asthma medication use. Asthma medication use was defined as positive if specific documentation was present in the admission or discharge note, or in the inpatient or outpatient electronic medication record, for use of bronchodilators, corticosteroids, or leukotriene inhibitors. Admission diagnoses were grouped in to broad categories reflecting the primary reason for admission. Patients admitted for an acute respiratory process were further classified according to whether the admitting team felt the child had status asthmaticus, bronchiolitis, croup, pneumonia or undefined respiratory distress.

Statistical analyses were performed using JMP® Pro 10 (SAS Institute Inc., Cary, NC). Fisher's exact test was used to compare groups on categorical variables and unpaired Student's *t*-test was used to compare groups on continuous variables. A significance criterion of 0.05 was used for all tests. Due to the exploratory nature of the study, corrections for multiple comparisons were not performed.

RESULTS

For the 31 samples sent to the CDC for EV-D68 testing and sequencing, there was 100% agreement between the results obtained in our laboratory and at the CDC (25 EV-D68

positive; 6 EV-D68 negative). The 6 EV-D68 negative specimens were identified by sequencing as Enterovirus 18, Coxsackievirus B2, Coxsackievirus A6, human Rhinovirus-A10 and human Rhinovirus-C. Of 17 EV-D68 positive tests where the GenMark RVP was performed, in each case sequencing confirmed the cross-reactivity with rhinovirus.

We compared asthma related presentation and discharge outcomes in the full cohort of 103 patients, which included 21 patients with EV-D68 and 82 patients with rhinovirus (Figure 1). Respiratory viral coinfection was common, especially among patients testing positive for rhinovirus, so a subanalysis was performed in the cohort of patients with no evidence of a respiratory viral coinfection, which included 19 patients with EV-D68 and 47 patients with rhinovirus.

Of the 103 patients all initially testing positive for rhinovirus on the GenMark eSensor® multiplex respiratory viral panel, 21 (20.4%) were EV-D68 positive and 82 (79.6%) were EV-D68 negative (Table 1, **Full Cohort**). All but three of the EV-D68 positive samples were isolated during the last three weeks of September 2014; the three additional positive samples were isolated over the subsequent 4 months. Compared to EV-D68 negative patients, EV-D68 positive patients were more likely to have a past history of asthma (33.3% vs. 11.0%, $P = 0.02$) or eczema (14.3 vs. 1.2%, $P = 0.03$). The frequency of chronic heart and lung disease or conditions resulting in immune compromise did not differ between the two groups. Patients positive for EV-D68 were more likely to have a documented history of leukotriene receptor antagonist (9.5% vs. 0%, $P = 0.04$) use, but the documented use of bronchodilators (61.9% vs. 41.5%, $P = 0.14$), inhaled steroids (28.6% vs. 17.1%, $P = 0.35$), oral steroids (23.8% vs. 10.9%, $P = 0.15$), antihistamine (14.3% vs. 2.4%, $P = 0.056$) and asthma medication overall (61.9% vs 42.7%, $P = 0.14$) did not differ.

The primary reason for hospital admission among both EV-D68 positive and negative patients was for an acute respiratory process (66.7% vs. 40.2%, $P = 0.048$). EV-D68 positive patients were more likely to present with status asthmaticus (47.6% vs 2.4%, $P < 0.001$). The proportion of EV-D68 positive vs negative patients with a primary diagnosis of bronchiolitis, croup, pneumonia or respiratory distress did not differ or was under powered to demonstrate a difference.

Upon admission EV-D68 positive patients had more wheezing (52.4% vs 24.4%, $P = 0.02$) and respiratory distress (90.5% vs 61.0%, $P = 0.02$). In hospital, EV-D68 positive patients were more likely to have lower respiratory involvement (85.7% vs 53.7%, $P = 0.01$) and to be treated with systemic steroids (57.1% vs 24.4%, $P = 0.007$) or leukotriene receptor antagonists (14.3% vs. 0%, $P = 0.008$). There was a trend toward increased bronchodilator (66.7% vs 43.9%, $P = 0.09$) and inhaled steroid (47.6% vs. 25.6%, 0.06) treatment in the EV-D68 positive patients. There was no significant difference with regard to intensive care admissions (52.4% vs 37.8%, $P = 0.32$), need for noninvasive or invasive ventilation (19.0% vs 23.2%, $P = 0.78$), or in the median number of days hospitalized, which was 3 days for both groups.

Compared to EV-D68 negative patients, EV-D68 positive patients were more likely to be discharged home on asthma medications (71.4% vs 40.2%, $P = 0.01$), including

bronchodilators (61.9% vs 35.4%, $P=0.045$), leukotriene receptor antagonists (19.0% vs 1.2%, $P=0.006$), inhaled steroids (47.6% vs 19.5%, $P=0.01$) and oral steroids (52.4% vs 15.9%, $P=0.001$).

Respiratory viral coinfection was more common in the EV-D68 negative group compared to the EV-D68 positive group (42.7% vs 9.5%, $P=0.005$). However, when a sub-analysis was performed that included only patients without a documented respiratory virus the overall findings were similar (Table 1, **No Coinfection**).

CONCLUSION

Epidemiologic data suggest that rhinoviruses are an important viral cause of seasonal asthma in children, however assays used in clinical and research laboratories to detect rhinoviruses typically fail to distinguish EV-D68^{3,4,6}. We used a specific rRT-PCR assay for EV-D68 to distinguish those patients infected with EV-D68 from those patients infected with rhinovirus, and performed a retrospective survey of asthma-related history, symptoms and treatment. The survey included 103 children admitted to our main hospital who initially tested positive for rhinovirus on a multiplex assay that did not distinguish EV-D68, and spanned a 16 month period that included the EV-D68 epidemic that occurred in the Fall of 2014. EV-D68 positive patients were compared to rhinovirus positive EV-D68 negative patients and were more likely to have a history of asthma or eczema, to have wheezing and respiratory distress on admission, to have status asthmaticus as their admission diagnosis, and to receive treatment with asthma medication in hospital and at discharge.

Our finding that respiratory viral coinfections were rare among EV-D68 positive patients suggests a direct role for EV-D68 in these patients' asthma related symptoms. In contrast, coinfection with another respiratory virus was common in patients with rhinovirus. This suggests that among hospitalized patients rhinoviruses may sometimes be asymptomatic bystanders. Indeed, while rhinovirus infections in young children are typically symptomatic, among college students asymptomatic infections outnumber symptomatic infections four to one^{7,8}. In a subanalysis excluding patients with a respiratory viral coinfection, the overall conclusions of our study were unchanged; EV-D68 positive patients were more likely to have a documented history of asthma, to present with status asthmaticus, and were more likely during the index admission to receive asthma medications in hospital and at discharge. Our study differs from a similar study out of St. Louis, in that we explored the role of respiratory viral coinfection⁹.

With the abrupt emergence in the Fall of 2014 of epidemic asthma associated with EV-D68, questions were raised as to whether EV-D68 might contribute to the well-documented seasonal surge in asthma admissions². While the possibility of a seasonal pattern exists, in our study EV-D68 was not observed either in the 9 months before the EV-D68 outbreak or in samples obtained after January 10, 2015, suggesting limited circulation outside of the outbreak period.

To better define the role of EV-D68 and rhinovirus in epidemic asthma, longitudinal studies that use EV-D68 analysis are necessary. It will be of particular interest to investigate the role

of specific respiratory viruses, including EV-D68 and specific strains of rhinovirus, as well as coinfection, in triggering asthma exacerbation or in predisposing infants to subsequent wheezing.

Acknowledgments

Shannon Rogers, William A. Nix and Steve Oberste from the Polio and Picornavirus Laboratory Branch, Division of Viral Diseases, Center for Disease Control are acknowledged for assistance in testing EV-D68 samples. Colleen Starkey is thanked for storing and tracking clinical samples.

Sources of support: This study was funded in part by a grant from the U.S. National Institutes of Health NHLBI RO1 HL-61007 to Dr. Giovanni Piedimonte.

References

1. Midgley CM, Watson JT, Nix WA, Curns AT, Rogers SL, Brown BA, Conover C, Dominguez SR, Feikin DR, Gray S, Hassan F, Hoferka S, Jackson MA, Johnson D, Leshem E, Miller L, Nichols JB, Nyquist AC, Obringer E, Patel A, Patel M, Rha B, Schneider E, Schuster JE, Selvarangan R, Seward JF, Turabelidze G, Oberste MS, Pallansch MA, Gerber SI. Severe respiratory illness associated with a nationwide outbreak of enterovirus D68 in the USA (2014): a descriptive epidemiological investigation. *Lancet Respir Med*. 2015; 3(11):879–887. [PubMed: 26482320]
2. Midgley CM, Jackson MA, Selvarangan R, Turabelidze G, Obringer E, Johnson D, Giles BL, Patel A, Echols F, Oberste MS, Nix WA, Watson JT, Gerber SI. Severe respiratory illness associated with enterovirus d68 - missouri and illinois, 2014. *MMWR Morb Mortal Wkly Rep*. 2014; 63(36):798–799. [PubMed: 25211545]
3. McAllister SC, Schleiss MR, Arbefeveille S, Steiner ME, Hanson RS, Pollock C, Ferrieri P. Epidemic 2014 enterovirus D68 cross-reacts with human rhinovirus on a respiratory molecular diagnostic platform. *PLoS One*. 2015; 10(3):e0118529. [PubMed: 25799541]
4. Gern JE. The ABCs of rhinoviruses, wheezing, and asthma. *J Virol*. 2010; 84(15):7418–7426. [PubMed: 20375160]
5. Nix WA, Oberste MS, Pallansch MA. Sensitive, seminested PCR amplification of VP1 sequences for direct identification of all enterovirus serotypes from original clinical specimens. *J Clin Microbiol*. 2006; 44(8):2698–2704. [PubMed: 16891480]
6. Enterovirus D68 2014 Real-Time RT-PCR Assay. Vol. 2016. Centers for Disease Control and Prevention; 2015.
7. Granados A, Goodall EC, Luinstra K, Smieja M, Mahony J. Comparison of asymptomatic and symptomatic rhinovirus infections in university students: incidence, species diversity, and viral load. *Diagn Microbiol Infect Dis*. 2015; 82(4):292–296. [PubMed: 25999242]
8. Peltola V, Waris M, Osterback R, Susi P, Ruuskanen O, Hyypia T. Rhinovirus transmission within families with children: incidence of symptomatic and asymptomatic infections. *J Infect Dis*. 2008; 197(3):382–389. [PubMed: 18248302]
9. Orvedahl A, Padhye A, Barton K, K OB, Baty J, Gruchala N, Niesen A, Margoni A, Srinivasan M. Clinical Characterization of Children Presenting to the Hospital with Enterovirus D68 Infection During the 2014 Outbreak in St. Louis *Pediatr Infect Dis J*. 2016

Figure 1.

Hospitalized Children Testing Positive for Rhinovirus on a Multiplex Respiratory Viral Panel Were Screened for Enterovirus D68 and Stratified According to Presence of Viral Coinfection. Children admitted to the hospital between December 2013 and March 2015 were screened for respiratory viral infections and banked samples that initially tested positive for rhinovirus were retrospectively tested for the presence of EV-D68. The multiplex respiratory viral panel used for screening did not distinguish between rhinovirus and EV-D68, as there was cross-reactivity. The full cohort (Table 1, **Full Cohort**) consists of 21 patients with EV-D68 and 82 patients with rhinovirus. Viral coinfection was detected by the multiplex panel, and was more common among patients with rhinovirus compared to patients with EV-D68 (42.7% vs. 9.5%, $P = 0.005$). A subanalysis was performed using only the 19 EV-D68 and 47 rhinovirus samples without evidence of viral coinfection (Table 1, **No Coinfection**).

Table 1

Presentation and Outcomes in Hospitalized Children with Enterovirus D68 or Rhinovirus, Full Cohort and No Respiratory Viral Coinfection Cohort

	EV-D68 Full Cohort N=21	Rhinovirus Full Cohort N=82	P value	EV-D68 No Coinfection N=19	Rhinovirus No Coinfection N=47	P value
Demographics						
Age years	4.06	2.79	0.17	4.6	2.03	0.63
Median (range)	(0.5–16.2)	(0.06–17.7)		(0.5–16.2)	(0.09–17.7)	
Male	15 (71.4%)	44 (53.7%)	0.22	13 (68.4%)	22 (46.8%)	0.17
Smoke exposure	3 (14.3%)	8 (9.8%)	0.69	3 (15.8%)	3 (6.4%)	0.34
Past History						
Asthma	7 (33.3%)	9 (11.0%)	0.02	7 (36.8%)	5 (10.6%)	0.02
Eczema	3 (14.3%)	1 (1.2%)	0.03	3 (15.8%)	1 (2.1%)	0.07
Chronic Heart or Lung Disease	6 (28.6%)	26 (31.7%)	1.00	6 (31.6%)	18 (38.3%)	0.78
Oncology, Transplant or Immunocompromised host	3 (14.3%)	16 (19.5%)	0.76	3 (15.8%)	13 (27.7%)	0.36
Medication History						
Bronchodilators	13 (61.9%)	34 (41.5%)	0.14	13 (68.4%)	20 (42.6%)	0.10
Inhaled Steroids	6 (28.6%)	14 (17.1%)	0.35	6 (31.6%)	7 (14.9%)	0.17
Antihistamines	3 (14.3%)	2 (2.4%)	0.056	3 (15.8%)	1 (2.1%)	0.07
Leukotriene receptor antagonist	2 (9.5%)	0	0.04	2 (10.5%)	0	0.08
Oral steroids	5 (23.8%)	9 (10.9%)	0.15	0	7 (14.9%)	0.10
Any Asthma Medication	13 (61.9%)	35 (42.7%)	0.14	13 (68.4%)	20 (42.6%)	0.10
Admission Diagnosis						
Acute Respiratory	14 (66.7%)	33 (40.2%)	0.048	14 (73.7%)	17 (36.2%)	0.007
Status Asthmaticus	10 (47.6%)	2 (2.4%)	<0.001	10 (52.6%)	2 (4.3%)	<0.001
Bronchiolitis	1 (4.8%)	18 (22.0%)	0.11	1 (5.3%)	5 (10.6%)	0.66
Croup	1 (4.8%)	1 (1.2%)	0.37	1 (5.3%)	0	0.29
Pneumonia	0	3 (3.7%)	1.00	0	3 (6.4%)	0.55
Respiratory Distress	2 (9.5%)	9 (11.0%)	1.00	2 (10.5%)	7 (14.9%)	1.00
Acute Neurologic	3 (14.3%)	7 (8.5%)	0.42	2 (10.5%)	2 (4.3%)	0.57
Fever in Special Populations	2 (9.5%)	21 (25.6%)	0.15	2 (10.5%)	11 (23.4%)	0.32

	EV-D68 Full Cohort N=21	Rhinovirus Full Cohort N=82	P value	EV-D68 No Coinfection N=19	Rhinovirus No Coinfection N=47	P value
Hematology and Oncology	0	8 (9.8%)	0.20	0	8 (17.0%)	0.09
Gastrointestinal	1 (4.8%)	3 (3.7%)	1.00	0	2 (4.3%)	1.00
Dermatologic	1 (4.8%)	2 (2.4%)	0.50	1 (5.3%)	0	0.29
Ear, Nose and Throat	0	3 (3.7%)	1.00	0	3 (6.4%)	0.55
Urinary Tract	0	2 (2.4%)	1.00	0	1 (2.1%)	1.00
Adenitis	0	1 (1.2%)	1.00	0	1 (2.1%)	1.00
Cardiac	0	1 (1.2%)	1.00	0	1 (2.1%)	1.00
Failure to Thrive	0	1 (1.2%)	1.00	0	1 (2.1%)	1.00
Signs on Admission						
Fever, > 38.4° C	12 (57.1%)	50 (61.0%)	0.80	11 (57.9%)	25 (53.2%)	0.79
Wheezing	11 (52.4%)	20 (24.4)	0.02	11 (57.9%)	11 (23.4%)	0.01
Respiratory distress	19 (90.5%)	50 (61.0%)	0.02	19 (100%)	31 (66.0%)	0.003
Hospital Course						
Length of admit, days Median (range)	3 (1-186)	3 (0-315)	0.86	3 (1-186)	3.5 (1-315)	0.58
Pediatric intensive care	11 (52.4%)	31 (37.8%)	0.32	10 (52.6%)	20 (42.6%)	0.59
Lower Respiratory Involvement	18 (85.7%)	44 (53.7%)	0.01	17 (89.5%)	22 (46.8%)	0.002
Noninvasive or invasive ventilation	4 (19.0%)	19 (23.2%)	0.78	4 (21.1%)	14 (29.8%)	0.55
Any Asthma Medication	15 (71.4%)	46 (56.1%)	0.22	15 (78.9%)	23 (48.9%)	0.03
Bronchodilators	14 (66.7%)	36 (43.9%)	0.09	14 (73.7%)	21 (44.7%)	0.055
Inhaled Steroids	10 (47.6%)	21 (25.6%)	0.06	10 (52.6%)	10 (21.3%)	0.02
Systemic Steroids	12 (57.1%)	20 (24.4%)	0.007	12 (63.2%)	13 (23.7%)	0.01
Inhaled Epinephrine	2 (9.5%)	17 (20.7%)	0.35	2 (10.5%)	6 (12.8%)	1.00
Leukotriene receptor antagonist	3 (14.3%)	0	0.008	3 (15.8%)	0	0.02
Medications at Discharge						
Any Asthma Medication	15 (71.4%)	33 (40.2%)	0.01	14 (73.7%)	20 (42.6%)	0.03
Bronchodilators	13 (61.9%)	29 (35.4%)	0.045	13 (68.4%)	17 (36.2%)	0.03
Leukotriene receptor antagonist	4 (19.0%)	1 (1.2%)	0.006	4 (21.1%)	1 (2.1%)	0.02
Inhaled steroids	10 (47.6%)	16 (19.5%)	0.01	10 (52.6%)	10 (21.3%)	0.02

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	EV-D68 Full Cohort N=21	Rhinovirus Full Cohort N=82	P value	EV-D68 No Coinfection N=19	Rhinovirus No Coinfection N=47	P value
Oral Steroids	11 (52.4%)	13 (15.9%)	0.001	11 (57.9%)	8 (17.0%)	0.002