Journal of Clinical Virology 70 (2015) 77–82

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Severe enterovirus 68 respiratory illness in children requiring intensive care management

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ARTICLE INFO

Article history:
Received 20 June 2015
Accepted 16 July 2015

Keywords:
Acute respiratory tract infection
Asthma
Enterovirus
EV-D68
Intensive care unit
Respiratory virus

ABSTRACT

Background: Enterovirus 68 (EV-D68) causes acute respiratory tract illness in epidemic cycles, most recently in Fall 2014, but clinical characteristics of severe disease are not well reported.
Objectives: Children with EV-D68 severe respiratory disease requiring pediatric intensive care unit (PICU) management were compared with children with severe respiratory disease from other enteroviruses/rhinoviruses.
Study design: A retrospective review was performed of all children admitted to Children's Mercy Hospital PICU from August 1-September 15, 2014 with positive PCR testing for enterovirus/rhinovirus. Specimens were subsequently tested for the presence of EV-D68. We evaluated baseline characteristics, symptomatology, lab values, therapeutics, and outcomes of children with EV-D68 viral infection compared with enterovirus/rhinovirus-positive, EV-D68-negative children.
Results: A total of 86 children with positive enterovirus/rhinovirus testing associated with respiratory symptoms were admitted to the PICU. Children with EV-D68 were older than their EV-D68-negative counterparts (7.1 vs. 3.5 years, $P = 0.01$). They were more likely to have a history of asthma or recurrent wheeze (68% vs. 42%, $P = 0.03$) and to present with cough (90% vs. 63%, $P = 0.009$). EV-D68 children were significantly more likely to receive albuterol (95% vs. 79%, $P = 0.04$), magnesium (75% vs. 42%, $P = 0.004$), and aminophylline (25% vs. 4%, $P = 0.03$). Other adjunctive medications used in EV-D68 children included corticosteroids, epinephrine, and heliox; 44% of EV-D68-positive children required non-invasive ventilatory support.
Conclusions: EV-D68 causes severe disease in the pediatric population, particularly in children with asthma and recurrent wheeze; children may require multiple adjunctive respiratory therapies.

1. Background

Enterovirus 68 (EV-D68) was identified from oropharyngeal swabs of 4 children hospitalized with acute lower respiratory tract illness (LRTI) in 1962 [1]. EV-D68 has features of both enteroviruses and rhinoviruses and is associated with respiratory symptoms [2,3]. Many multiplex PCR assays used in clinical practice do not distinguish between the two species, so the manifestations and severity of EV-D68 have not been well characterized. Previous epidemiologic studies have been primarily retrospective [4–7], and rates of detection have been <1% [7,8]. Although the majority of infections were in children [8,9], pediatric cohorts were small, usually less than 15 patients [5,10,11]. In mixed adult and pediatric cohorts,

Abbreviations: EV-D68, enterovirus 68; PICU, pediatric intensive care unit; LRTI, lower respiratory tract illness; ICU, intensive care unit; CDC, Centers for Disease Control and Prevention; RPP, respiratory pathogen panel; CMH, Children's Mercy Hospital; NIV, non-invasive ventilation; IQR, interquartile range; ANC, absolute neutrophil count; ALC, absolute leukocyte count; RAD, reactive airway disorder; AFM, acute flaccid myelitis.

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http://dx.doi.org/10.1016/j.jcv.2015.07.298
1386-6532/

underlying medical conditions were common [12,13]. Intensive care unit (ICU) stays were rare [5,11,14], and in reports of severe disease, cohorts contained less than 5 patients [4,13].

EV-D68 infections generally occur in the late summer-early fall months and in unpredictable epidemic cycles [5,7,14–16]. Prior to 2006, EV-D68 was rarely identified. The National Enterovirus Surveillance System, a voluntary passive surveillance mechanism through the Centers for Disease Control and Prevention (CDC), reported 26 cases from 1970 to 2005. EV-D68 accounted for 0.1% of reported enteroviruses during that period [16]. Between 2008 and 2010, multiple countries reported EV-D68 outbreaks or clusters [4,7,10,13,17]. After 2010, EV-D68 was again rarely reported until Fall 2014 when a resurgence of EV-D68 disease was identified in the United States and Europe [18–20].

2. Objective

We aim to describe severe EV-D68 disease, including at-risk populations, presenting symptoms, and extent of intensive therapies used compared with children with severe disease from other enteroviruses/rhinoviruses. We report the largest cohort of pediatric EV-D68 disease to date, and the first to focus on children requiring pediatric ICU (PICU) stay.

3. Study design

3.1. Study subjects

An increase in emergency department visits and hospital admissions associated with severe respiratory disease was noted on August 15, 2014 at Children's Mercy Hospital (CMH). A case definition was established on August 21, and respiratory pathogen panel (RPP) (Biofire Inc, Salt Lake City, Utah) testing was recommended for all inpatient children with increased work of breathing requiring supplemental oxygen or continuous albuterol. This assay does not distinguish between human enteroviruses and rhinoviruses [21]. Patients, aged 0–17 years, admitted to CMH with multiplex RPP testing positive for enterovirus/rhinovirus from August 1 to September 15, 2014 were retrospectively identified. Testing for EV-D68 was done after the patient encounter, so results were unavailable to the clinician. Patients requiring hospitalization in the PICU were identified from the larger cohort by chart review. CMH's Institutional Review Board approved the study.

3.2. Virologic testing

Prior to the development of real-time RT-PCR for EV-D68 [22], samples were sequenced based on the enterovirus VP1 region at the CDC [23]. Once an EV-D68-specific RT-PCR method was developed, the remaining samples were tested by RT-PCR only at CMH. Total RNA was extracted [24] and tested per CDC protocol with minor modification of the probe to use 5-Cy5 dye [25]. All primers and probes were purchased from IDT DNA Inc (Coralville, IA).

3.3. Patient data

Chart review was performed, and data were entered into a standardized document in REDCap [26]. Laboratory and radiographic values were the first documented results, from either CMH or the transferring hospital. Treatments included only therapies administered at CMH. Non-invasive ventilation (NIV) was defined as high flow nasal cannula >5 l/min, continuous positive airway pressure, or biphasic positive airway pressure.

Table 1
Demographic characteristics of PICU children with EV-D68 and with other enteroviruses/rhinoviruses.

	EV-D68 positive $N=59$	EV-D68 negative $N=24$	P value[a]
Median age (IQR) – years[b]	7.1 (3.0–11.5)	3.5 (0.9–7.8)	0.01
Male sex – no. (%)	39 (66)	18 (75)	0.43
Race or ethnic group – no. (%)[c]			0.28
White	25 (42)	14 (58)	
Black	20 (34)	5 (21)	
Hispanic or Latino	8 (14)	1 (4)	
Other/unknown	6 (10)	4 (17)	
High risk condition – no. (%)			
Asthma	30 (51)	8 (33)	0.15
Recurrent wheeze	10 (17)	2 (8)	0.49
Asthma or recurrent wheeze	40 (68)	10 (42)	0.03
Neurologic	5 (9)	5 (21)	0.14
Prematurity	4 (7)	5 (21)	0.11
Cardiac	1 (2)	2 (8)	0.20
None	12 (20)	6 (25)	0.64

[a] P values were calculated by Pearson chi-square or Fisher's exact test, except for median age, which was calculated by Wilcoxon rank-sum test.
[b] IQR denotes interquartile range.
[c] Race and ethnic group were determined according to parental/guardian report in the medical record.

3.4. Statistical analysis

Nominal variables were described using total number and percentage with Pearson Chi-square test, or Fisher's exact test, to determine significance between the groups. Continuous variables were described by median with interquartile range and Wilcoxon rank-sum test. All statistics were performed in SPSS (versions 18.0 and 20.0).

4. Results

From August 1 to September 15, 2014, 562 children were admitted to CMH, had positive enterovirus/rhinovirus testing, and had specimens available for EV-D68 testing. 61/341 (17.9%) EV-D68 positive (EV-D68+) children required PICU management compared with 34/221 (15.4%) children with non-EV-D68 enteroviruses/rhinoviruses (EV-D68-). Of the 95 PICU children, 10 EV-D68- children and 2 EV-D68+ children were excluded because they required PICU management for non-respiratory reasons. Thus, 83 children were included in the final analysis: 59 EV-D68+ children and 24 EV-D68- children (Fig. 1).

4.1. Baseline characteristics

EV-D68 + patients were significantly older than EV-D68- patients (7.1 vs. 3.5 years, $P=0.01$) (Table 1). The majority of patients were male. No statistically significant racial differences were noted. Approximately, 55% of both groups had publicly funded insurance.

Among EV-D68+ patients, 40 (68%) had a history of asthma or recurrent wheeze, compared with 10 (42%) of EV-D68- children, $P=0.03$. Other chronic medical conditions were not significantly different between the two groups. Twelve (20%) EV-D68+ patients had no reported high-risk condition. No differences in household smokers or daycare/school exposure were noted.

4.2. Clinical signs and symptoms

Length of illness prior to presentation was not different between EV-D68+ and EV-D68- children (2 vs. 1.5 days, $P=0.83$). Respiratory symptoms were prominent in both groups (Table 2). Cough was the only parent-reported symptom significantly different between EV-