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Clinical Severity of Influenza-like Illness due to Coxsackievirus/Echovirus: A Case-Series Analysis

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Introduction

- Acute respiratory infections (ARI) have been a significant source of disease and non-battle injury (DNBI) among military forces for centuries. Whether it is a well-known and relatively high-impact threat such as influenza, or the cumulative burden of tens of thousands of soldiers with the common cold, there are few threats to the fighting force with more potential to affect readiness at a population level than respiratory infections. Because ARI can interrupt training cycles and compromise operational readiness, understanding of disease etiology and effective ARI prevention strategies for military populations are critically needed.
- While most preventions and treatments focus on pathogens, such as influenza virus and adenovirus, limited information is available on other viral respiratory pathogen, such as coxsackievirus/echovirus which also cause work and training days lost.
- We examined characteristics associated with coxsackievirus/echovirus (CV/EV) detection and compared clinical severity of CV/EV patients to influenza patients to understand the relative impact of such pathogens.

Methods

- Since 2009, we enrolled otherwise healthy military personnel and beneficiaries into an observational, longitudinal study of influenza-like illness (ILI) at five military treatment facilities across the continental United States (Figure 1).

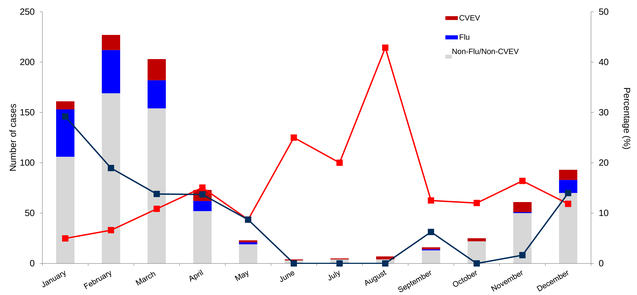
Figure 1. Clinical sites participating in the ARIC Natural History Study

- Eligibility. Patients presenting for care <72h after the onset of ILI, defined as fever (temperature of 100.4° F or greater at the time of evaluation, or by self-report) and sore throat or one of the following respiratory symptoms: cough, sputum production, shortness of breath, or chest pain. Patients with underlying medical conditions were excluded.
- Clinical and demographic information, and a nasopharyngeal swab was collected at baseline (day 0). Participants returned on days 3±1, 7±2 and 28±7; a daily symptom diary was completed for the first seven days following ILI onset. Symptom presence and severity was recorded either by self-report (diary) or interview as: 0 (none); 1 (mild: not changing activity or requiring treatment); 2 (moderate: requiring some modification in activity and/or medication); and 3 (severe: incapacitating, unable to perform normal activities, requiring bed rest and/or medication). Participants were trained by research personnel on the definitions of each score. Swabs were tested for influenza by real-time reverse transcription polymerase chain reaction (rtRT-PCR) at the Naval Health Research Center (San Diego, CA).
- A target-enriched multiplex PCR (TEM-PCR) panel for 13 bacterial and 10 viral respiratory pathogens was developed by Diatherix Laboratories, LLC. (Huntsville, AL). The platform relies upon nested multiplex PCR to provide the initial target enrichment and super primers to amplify and label the PCR products The viral respiratory pathogens on the panel include: adenovirus, coxsackievirus/echovirus, bocavirus, coronavirus, human metapneumovirus, rhinovirus, influenza A/B, parainfluenza and respiratory syncytial virus.
- We measured presence of a symptom at any severity level (mild, moderate and severe); further stratified comparisons were based on moderate/severe versus none/mild, and severe versus mild/moderate/none. Composite measures were the sum of individual symptom scores in the following categories: (1) lower respiratory symptoms: cough, breathing difficulty, hoarseness and chest pain, (2) upper respiratory symptoms: earache, runny nose, sore throat and sneezing; (3) systemic symptoms: chills, muscle ache, headache and fatigue; (4) total symptoms: sum of the above three categories.
- Statistical analyses were performed using SAS (Version 9.3; SAS Institute, Cary, NC) and R Package (version 3.1.3 for Windows). The study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences (IDCRP-045).

Results

- From 2009-2014, a sample of 898 cases with ILI were tested for viral respiratory pathogens using Diatherix multiplex respiratory pathogen panel. Of these, 89 (9.9%) had detection of coxsackievirus/echovirus. Children were more likely to have CVEV detection compared to adults (14.7% vs. 8.0%, p<0.01).
- Forty-six (51.7%) cases with CVEV had co-detection of other viral respiratory pathogens, including human rhinovirus (78%), human metapneumovirus (13%), RSV (13%), coronavirus (9%), and parainfluenza virus (4%), and influenza (4%).
- Proportion of CVEV detection increased in March and was high in late spring and summer, while detection of influenza virus peaked in winter season (December to February). (Figure 2)

Figure 2. Number of cases with detection of influenza and CVEV



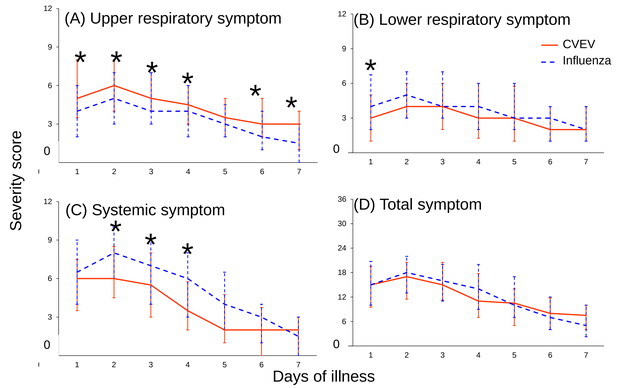
- When compared to cases with influenza, CVEV cases were more likely to be children, children attending daycare center and adults who currently smoked.

Table 1. Comparison of characteristics between ILI patients with influenza virus and CVEV

Variables	CVEV-positive	Flu-positive	p-value
Age (year)	N (%)	N (%)	
0-17	38 (43.7)	33 (23.1)	P<0.01
18-65	49 (56.3)	110 (76.9)	
Sex			
Male	44 (50.6)	76 (53.1)	0.70
Female	43 (49.4)	67 (46.9)	
Season			
2010-11	36 (41.4)	30 (21.0)	P<0.01
2011-12	28 (32.2)	24 (16.8)	
2012-13	6 (6.9)	47 (32.9)	
2013-14	17 (19.5)	42 (29.4)	
Smoking status in patients aged 13 and older			
Current	16 (32.7)	15 (13.4)	0.02
Former	7 (14.3)	21 (18.8)	
Never	26 (53.1)	76 (67.9)	
Index attending daycare? (children only)			
No	16 (42.1)	26 (78.8)	P<0.01
Yes	22 (57.9)	7 (21.2)	

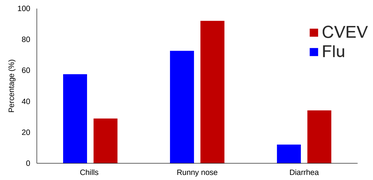
- Adults with CVEV reported higher severity score of upper respiratory symptoms through the first 7 days of illness compared to those with influenza virus. On the contrary, adults with influenza virus reported higher scores on systemic symptoms than adults with CVEV. (Figure 3)

Figure 3. Clinical severity of CVEV compared with influenza among adults (*: p<0.05)



- Similarly, the reported frequency of runny nose (p<0.01) and diarrhea (p<0.05) was higher among children with CVEV vs. influenza infection, whereas the reported frequency of chills was higher among those with influenza (p<0.01, Figure 4)

Figure 4. Prevalence of symptoms at enrollment among children with CVEV vs. influenza infection



Conclusions

- Overall, CVEV represented a small proportion of ILI and was prevalent in post-influenza season.
- CVEV causes more severe upper respiratory tract symptoms in both adults and children, but less severe systemic symptoms compared to influenza virus.
- Studies of severe ILI among adults should assess the contribution of CVEV, especially in the post-influenza season.

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