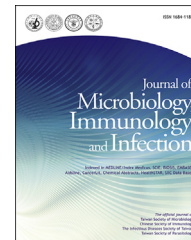




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ORIGINAL ARTICLE

# Predicting severe enterovirus 71 infection: Age, comorbidity, and parental behavior matter



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## KEYWORDS

developmental delay;  
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hand hygiene;  
herpangina;  
risk factors

**Objective:** Enterovirus 71 (EV71) is one of the major pathogens that cause severe enteroviral infections. Our aim was to study the behavioral and household risk factors for its serious complications.

**Methods:** Between May 2011 and November 2012, we enrolled children who had symptoms of EV71 infection from six hospitals in Taiwan. The caregivers of each patient were interviewed to determine their hand hygiene habits in relation to EV71 infection. The severity of EV71 infection was classified as follows: Stage 1, hand–foot–mouth disease or herpangina; Stage 2, meningitis or myoclonic jerk; Stage 3A, encephalitis; Stage 3B, cardiopulmonary failure. Stages 2 to 3B were defined as severe EV71 infection. Children with Stages 3A and 3B infection were designated as the critical group.

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**Results:** A total of 399 patients had laboratory-confirmed EV71 infection. Three risks factors were associated with the different degrees of severity in EV71 infection. Children <2 years old had much greater risks for severe EV71 infection [odds ratio (OR) 1.8; 95% confidence interval (CI), 1.2–2.8], delayed medical evaluation for critical infection (OR 9.4; 95% CI, 3.6–24.1), and developmental retardation for cardiopulmonary failure (OR 8.3; 95% CI, 2.0–33.7). Among all the habits and household factors, caregivers in the critical group had a significantly lower rate in terms of cleaning the faucet after washing their hands (OR 2.63; 95% CI, 1.14–6.08).

**Conclusions:** Children <2 years old, developmental retardation, and delayed medical intervention were associated with severe EV71 infection. Cleaning water faucets after hand washing was a protective habit that reduced the risk of complications.

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## Introduction

Enterovirus 71 (EV71), which belongs to the Picornaviridae family, induces both hand–foot–mouth disease (HFMD) and herpangina.<sup>1</sup> Compared with other enteroviruses, EV71 is notorious for its severe neurological and systemic complications, specifically in young children.<sup>2–5</sup> Unfortunately, little is known about the predisposing factors for these critical complications, which makes it more difficult to prevent this easily transmitted infection. Although most patients may fully recover from HFMD, the high mortality rate exacts a dreadful toll, especially when an unfavorable outcome occurs.<sup>2,6</sup> Early recognition of the critical symptoms and improving supportive management are the main strategies adopted to lower the morbidity and fatality rates among the infected patients.<sup>3,7–10</sup>

Several risk factors have been reported in enterovirus (EV) epidemiological studies. For instance, children younger than 3 years and those who attended kindergarten were significantly predisposed to EV71 infection.<sup>11–13</sup> However, these results only suggested susceptible hosts to enteroviral infection, and failed to point out the risks of serious complications. Hand hygiene was proposed to reduce the chances of contracting HFMD and herpangina, but its effectiveness in preventing severe complications is still unknown.<sup>1,14</sup> Moreover, the daily activities of young children are heavily dependent on their caregivers, which indicates that the adults' behavior may greatly affect the children's health. Thus, we conducted a multi-institutional study in three different areas in Taiwan between 2011 and 2012. By interviewing the caregivers, we analyzed the factors associated with the patients' clinical outcomes, such as awareness of severe symptoms, basic knowledge of EV infection, and personal hygiene. We hope that the results will encourage the public to modify their behavior or living environment in order to decrease the risks of EV71 complications.

## Material and methods

### Setting and case definition

We enrolled children in six hospitals, which are located in three major metropolitan areas (Taipei, Taichung, and

Kaohsiung) in Taiwan. These facilities included three tertiary hospitals and three regional hospitals, representing 600 pediatric beds in total. This study was approved by the institutional review boards in all six hospitals. Between May 2011 and November 2012, children exhibiting symptoms of EV infection, either HFMD or herpangina, were enrolled. Signed consent forms were obtained from the patients' guardians. Patients were included for further analysis if the pathogens were confirmed to be EV71 by virological tests and when informed consent forms had been duly obtained. At the outset, we classified EV71 cases into four categories.<sup>2–5</sup> Uncomplicated children had mild symptoms (e.g., HFMD, herpangina, or fever) without any central nervous system (CNS) or systemic involvement (Stage 1). Children with severe EV71 infection, by contrast, presented neurological or systemic symptoms. These conditions included myoclonic jerk or meningitis (Stage 2), encephalitis (Stage 3A), and CNS involvement with cardiopulmonary failure (Stage 3B). Those having encephalitis or cardiopulmonary failure (Stages 3A and 3B) were defined as the critical group.

### Interview and records

We interviewed each participant's caregiver(s) during the enrollment stage of our study. The following aspects were investigated: patients' demographic data, socioeconomic status of the family, residential and childcare conditions, the caregivers' awareness regarding EV71 infection, and their hand hygiene habits.

### Laboratory methods

Two throat swabs were collected from each patient for viral isolation and molecular typing (real-time reverse transcription polymerase chain reaction). If the child has symptoms lasting for more than 4 days prior to enrollment, two additional rectal swabs would be collected for identification of viral etiology. A detailed description of the methods and materials has been delineated in our previous studies.<sup>15,16</sup> EV71 infection was confirmed on the basis of positive results from viral isolation with or without positive EV71 VP1 typing.

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