Epidemiology, Transmission, and Clinical Management of EV71 Infections

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EV71 outbreak in Taiwan in 1998 is very well-known to cause a lot of fatal children cases. In 1998 epidemic, there were 405 severe cases with 78 deaths. Thereafter, EV71 still circulates periodically in Taiwan as well as in mainland China where hundreds of fatal cases were found each year.

Several risk factors have been reported in enterovirus epidemiology studies. For instance, children younger than 3 year-old and attending kindergarten were significantly associated with EV71 infection, and those with EV71 seropositivity and living in rural areas had greater risks of severe HFMD. We studied 433 family members from 94 families in which EV71 positively isolated. The overall enterovirus 71 transmission rate of household contacts was 52% (176/339): 84% (70/83) siblings, 83% (19/23) cousins, 41% (72/175) parents, 28% (10/36) grandparents and 26% (5/19) uncles/aunts. So, enterovirus 71 household transmission rates are high for children, medium for parents and low for other adults. Among 87 infected adults, 53% (46/87) were asymptomatic, 39% (34/87) had nonspecific illnesses of fever, sore throat or gastrointestinal discomfort and only 8% (7/87) had hand, foot and mouth disease.

According to our clinical studies, symptomatic enterovirus 71 (EV71) infection can progress through four stages: HFMD/herpangina (Stage 1), CNS involvement (Stage 2), cardiopulmonary failure (Stage 3), and convalescence (Stage 4). Most EV71 cases in those studies stayed at stage 1, some progressed to Stage 2 and a few would advance to the most severe condition, Stage 3. A stage-based management was thus developed to reduce the case-fatality but most survivors of brainstem encephalitis plus cardiopulmonary failure might have neurologic sequelae and impaired cognition. Patients with Stage 1 required treatment of symptoms only. Patients identified as having Stage 2 were hospitalized and their treatment included fluid restriction and administration of osmotic diuretics for those with signs of increased intracranial pressure (IICP) and furosemide for those suspected having fluid overload. Intravenous immunoglobulin (IVIG) was administered and blood pressure, oximeter, coma scale and blood sugar were closely monitored. Patients were managed in the ICU if they were found to have tachypnea/apnea, hypertension/hypotension, signs of IICP, or hyperglycemia. Patients identified as having Stage 3 were identified when they required ventilator support and inotropic agents. We subdivided these patients into Stage 3A as having hypertension and pulmonary edema and Stage 3B as having hypotension. Treatment of Stage 3 A was as follows: their intensive care management included continuous fluid restriction, administration of milrinone to control severe hypertension and to increase cardiac output, early intubation with positive pressure mechanical ventilation with increased positive end expiratory pressure for pulmonary edema. High frequency oscillatory ventilator was considered if pulmonary edema or hemorrhage persisted or if they developed severe hypoxemia. When a patient's blood pressure drops below the normal range for his or her age, the disease was considered to be in stage 3B. In some cases, blood pressure is very unstable, requiring fine adjustments of inotropic agents such as dopamine and epinephrine and even ECMO. For Stage 4 patients, rehabilitation is provided for limb weakness/atrophy, dysphagia, diaphragm dysfunction, apnea or central hypoventilation.

In our follow-up study of severe EV71 cases, 18 (64%) of the 28 cases with cardiopulmonary failure after CNS involvement had limb weakness and atrophy, 17 (61%) required tube feeding, and 16 (57%) required ventilator support. Delayed neurodevelopment was found in only 1 (5%) case with severe EV71 CNS involvement and in 21 (75%) cases with cardiopulmonary failure ($p<0.001$). Children with cardiopulmonary failure after CNS involvement scored lower on

intelligence tests than children with CNS involvement alone (p=0.003). Among patients with CNS involvement alone, children infected at ages younger than 2 had lower verbal comprehension than children infected at older ages (p=0.009). EV71 CNS involvement with cardiopulmonary failure may be associated with neurological sequelae, delayed neurodevelopment and reduced cognitive functioning. Children with CNS involvement without cardiopulmonary failure did well in neurodevelopment.