

Clinical Characteristics of an Outbreak of Hand, Foot and Mouth Disease in Singapore

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Abstract

Background: We experienced a hand, foot and mouth disease (HFMD) outbreak in late year 2000 in Singapore. Between 14 September 2000 and 14 November 2000, a total of 3526 cases of HFMD were notified. There were 652 patients clinically suspected to have HFMD, who were seen at the Children's Emergency department of KK Women's and Children's Hospital of Singapore. **Objective of the study:** To study the clinical profile and virologic isolates of children admitted with HFMD during the outbreak. **Study design:** A prospective observational study. **Methods:** Analysis of clinical features and virologic studies of 129 selected cases of HFMD and herpangina. **Results:** The median age was 25 months with a range of between 4 months and 11 years. The majority were less than 5 years old (87%). The male-to-female ratio was 1.3:1. The median numbers of day of illness to presentation to the hospital was 3 days. Poor feeding and loss of appetite accounted for 76.7% of the admissions. Symptoms of vomiting were present in 37.2% of the cases. Oral ulcers were found in 96.1%, rashes over hands in 87.6%, over feet in 86.8% and over buttocks in 54.3%. Only 4.7% exhibited no rashes other than oral ulcers and were labelled as herpangina. The median duration of fever was 3 days, ranging from 2 to 7 days. An intravenous drip was required in 68.2% due to poor feeding. Viral cultures were sent in 89.1% of patients of whom 61.7% of patients were positive for viruses. Of the positive cultures, types of viruses isolated were EV71 (enterovirus 71) in 59/71 (83%), Coxsackievirus (A16, A24, A2 B3, B4) in 6/71 (8.4%), EV Untypable in 4/71 (5.6%) and mixed [EV71, echo25, cytomegalovirus (CMV)] in 2/71 (2.8%). EV71 was isolated mostly from stool samples followed by vesicle fluid culture and throat swabs. Two siblings aged 14 months and 2.5 years died during this period at day 5 of illness, their post-mortem examinations showed interstitial pneumonitis of the lungs. EV71 was isolated from the brain, heart, tonsils, intestines, throat and rectal swabs. A raised total white cell count of 14,000/L versus 12,000/L was significantly associated with complicated HFMD ($P = 0.04$). There was no difference in clinical characteristics of EV71 versus non-EV71 infections. Other viral illnesses, e.g. measles and CMV, may be mistaken for HFMD in the outbreak setting. **Conclusions:** HFMD tends to occur in younger children less than 5 years old due to low herd immunity. Poor feeding due to mouth ulcers accounts for admission to hospital requiring intravenous drip. EV71 accounted for the majority (75%) of the positive isolations, followed by coxsackievirus and untypable EV, mixed infection of echovirus or CMV. The yield of virus isolation was highest from stool, followed by vesicles and throat swabs. There is no difference in clinical characteristics of EV71 and non-EV71 virus infections. Enterovirus can cause mild symptoms to fatal death. Two infants died of interstitial pneumonitis and encephalitis.

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Introduction

The enterovirus family causes a wide array of illnesses, some easily recognised clinically and others diagnosed as non-specific viral illnesses. This large family of viruses, composed of more than 70 serotypes, accounts for at least 10 to 15 millions of asymptomatic infection per year in the United States.¹⁻³ The majority of enterovirus infection are benign and manifested by fever alone or as hand foot and mouth disease (HFMD) or herpangina.⁴ The same viruses

that cause these common asymptomatic viral illness, can cause severe and life threatening infections such as meningitis, myocarditis, encephalitis, neonatal sepsis and polio. Enterovirus infection may mimic bacterial disease which often leads to unnecessary antibiotic use and investigations.⁴

The enterovirus, a member of the picornavirus family, includes coxsackieviruses A and B, echoviruses, EV (enterovirus) 68 to 71 and polioviruses. Typically, only a

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few serotypes of enteroviruses cause infections in any given year and certain serotypes are more likely to cause disease than others. Collectively, these viruses can infect all tissues of the body. Individual members of the group have tropism for certain tissue, e.g. coxsackie B viruses often infect the heart, EV71 and 70 are neurotropic; however, such tropism is neither unique nor specific.⁴ Due to the shortage of adequate viral diagnostic laboratories and difficulty in isolation of some strains like coxsackie A, reports of enteroviruses may only represent the tip of the iceberg.⁵

Since it was first recognised in California in 1969,^{5,6} EV71 infections have been reported in at least 12 small and large outbreaks throughout the world. At least 4 outbreaks of EV71 infections that caused more than 20 deaths occurred in Bulgaria in 1975,⁷ Hungary in 1978,⁸ Malaysia in 1997⁹ and Taiwan in 1998.¹⁰ In Malaysia and Taiwan, most of the patients who died had HFMD or herpangina and died of pulmonary oedema and brain stem encephalitis.¹⁰ We describe here the HFMD cases that were admitted to KK Women's and Children's Hospital (KKWCH) during an outbreak from September to November 2000.

Material and Methods

Clinical Definitions

HFMD: A case of HFMD was defined as a papular, vesicular or macular rash on hands, feet and/or buttocks, and/or associated with mouth ulcers.⁴

Complicated HFMD: A case of HFMD which required admission to intensive care for monitoring due to abnormal clinical findings and/or was fatal.

Herpangina: is a vesicular enanthem of the oropharynx, often accompanied by fever, sore throat and pain on swallowing.²

We analysed all cases with clinical features suggestive of HFMD and herpangina who were admitted to KKWCH between mid September and mid November 2000. A total number of 3526 cases were notified to the Ministry of the Environment during this period.¹¹

A structured questionnaire was designed and used for the collection of data on clinical presentations and laboratory investigations of enrolled cases in the study. Data on demographic, clinical characteristics and virological isolates for the 129 cases admitted with HFMD or herpangina and were analysed. The demographic data collected included age, sex, race, source of referral and district of residence of the patients. The clinical characteristics included contact history, attendance at play school, the day the child presented to the hospital, indication for admission, maximum temperature and the days fever lasted, presence of vomiting and any other abnormal clinical examination findings. The

site and morphology of rash and presence of mouth ulcers were also noted. Investigations like full blood count, serum electrolytes and virologic isolates from stool, vesicles and throat swabs were collected and analysed.

Isolation and Identifications of Enterovirus

Method: Samples were obtained from oral ulcers, vesicular lesions and stool for isolation of enterovirus. Post-mortem samples were also sent from brain, heart, lung, tonsil, lymph node, spleen and intestine tissues for viral culture. Samples were submitted to Department of Pathology, Singapore General Hospital for virus isolation. The samples were inoculated into HeLa, Hep-2, human embryonic lung fibroblasts (HEL) and human rhabdomyosarcoma (RD) cells. The cultures were incubated at 36°C and examined daily for cytopathic effects (CPE) for up to 21 days, with blind passages at weekly intervals.

Enteroviruses were identified by neutralisation tests¹² using Lim Benyesh-Melnick (LBM) A-H antiserum pools (WHO collaborating centre for virus reference and research, Statens Serum Institute, Copenhagen, Denmark), equine antiserum pools from National Institute of Public Health and the Environment, Bilthoven, Netherlands, as well as 385JS polyclonal antiserum specific for EV71 from Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia. Enteroviruses that could not be typed with these antisera were considered untypable. Cytomegalovirus (CMV) was confirmed with IFA as described¹³ using fluorescein isothiocyanate labelled monoclonal antibodies to CMV (Bartels CMV DFA kit, Issaquah, USA).

Statistical Analysis

The data were analysed using SPSS program (SPSS Chicago, IL).

The chi-square test was used to compare categorical data and Mann-Whitney U test for continuous non-parametric data. Linear regression was used in a multivariate analysis to identify risk factors for poor outcome in HFMD patients. *P* values of less than 0.05 were considered statistically significant. The statistician was consulted for statistical analyses.

Results

A total of 3526 cases were notified to the Ministry of the Environment during this period, of which 652 cases were seen and clinically diagnosed as HFMD at the children's Emergency Department of KKWCH. Of this, 139 (21%) were admitted due to poor feeding from mouth ulcers, vomiting or high fever. Ten patients were later excluded because of diagnoses of measles in 7 cases, which was confirmed later by immunofluorescence, CMV in 2 cases and Kawasaki disease in 1 case.

Out of the 129 selected cases, 99 (76.7%) were self-referred and 30 (23.3%) were referred by family physicians. The median day when the patient presented with HFMD was on day 3 (range, day 1 to 7). The median age of the patients was 25 months, with a range of 4 months to 11 years. A total of 87.6% were less than 5 years of age. The majority (58.9%) were male, with a male-to-female ratio of 1.3:1. The highest incidence rate was among Chinese (70%) followed by Malays (27%) and Indians (3%). In contrast to the ethnic distribution in Singapore which is Chinese (76%), followed by Malays (14%), Indians (7.7%) and others (1.4%). The Malays incidence rate of 27% is twice the ethnic distribution of Malays (14%) in Singapore. Most of the children (95.3%) had HFMD and 4.7% had herpangina. Playschool/kindergarten/day-care centre attendance was documented in 26.4% of the patients, while 43.4% had a positive contact history either with siblings or at playschool centres. The total duration of fever was 3 days, with a range of 1 to 7 days. Mouth ulcers were seen in 96.1% cases. Papular-vesicular rashes were seen on the hands in 79.1%, feet in 77.5% and buttocks in 52%. Only vesicular rashes were seen in 16.3% of cases. A total of 68.2% of patients needed an intravenous drip. Concurrently, 23.7% had abnormal physical findings during admission including tachycardia without fever (2.3%), hypertension (0.8%), red eye (1.6%), hematemesis (0.8%) and drowsiness (0.8%). The age, sex, race, residential district, presence of vomiting, site and morphology of the rash, duration or degree of fever was not different between complicated and stable HFMD and EV71 and non-EV71 virus infection.

Clinical characteristics of the patients according to age are shown in Table I.

A total 179 samples from 115 patients (89%) were sent

from stools, vesicles or oral swabs for virus isolation; of which 96/179 (53.6%) samples were positive for enterovirus. These comprised EV71 in 83% (59/71), coxsackievirus in 8.4 % (6/71) and EV untypable in 5.6% (4/71). The virology results are shown in Table II. The virus isolation was highest from stool (74.6%), followed by vesicle (51.7%) and throat swabs (39%).

HFMD-related Deaths

During this period, there were 7 HFMD-related admissions to the intensive care unit (ICU) of which 2 patients died. Both were siblings.

The first case was a 14-month-old Chinese girl who presented on day 3 with fever, rashes and vomiting. On admission she was alert with signs suggestive of HFMD with rashes over hands, feet and perianal region with oral ulcers. The result of routine haematology revealed normal cell count of $14.4 \times 10^9/L$ (reference range, 6.0-17.5), elevated neutrophil count of $12.1 \times 10^9/L$ (1.5-8.5), lowered lymphocyte count of $334 \times 10^9/L$ (150-450). On the second day of admission she was noted to be lethargic and dehydrated. She was started on intravenous fluids with close blood pressure monitoring. A repeat haematology was essentially the same (elevated neutrophils of 10.51, lymphocytes of 1.73). A routine biochemistry was normal. Blood culture was taken and she was started empirically on intravenous ceftriaxone to cover possible bacterial infection. On the same day she was found to be unresponsive and had poor perfusion. She developed hypotension requiring fluid flush and inotropic support. An urgent computed tomographic (CT) scan was done and was normal. Chest X-ray showed right upper lobe pneumonia. The coagulation profile showed a prolonged prothrombin time (PT) of

TABLE I: CLINICAL CHARACTERISTICS ACCORDING TO AGE

Age	<1 year (n = 20)		1-5 years (n = 93)		>5 years (n = 16)		Total (n = 129)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Male	13/20	(65)	58/93	(62.4)	5/16	(31.3)	76/129	(58.9)
Female	7/20	(35)	35/93	(37.6)	11/16	(68.8)	53/129	(41.1)
Preschool [#]	1/20	(5)	26/93	(27.9)	7/16	(43.8)	34/129	(26.4)
Contact history	10/20	(50)	34/93	(36.6)	12/16	(75)	56/129	(43.4)
Poor feeding/Loss of appetite	17/20	(85)	73/93	(78.5)	9/16	(56.3)	76/129	(58.9)
Vomiting	6/20	(30)	3/93	(3.2)	9/16	(56.3)	48/129	(37.2)
Mouth ulcers	20/20	(100)	88/93	(94.6)	16/16	(100)	124/129	(96.1)
Intravenous drip	14/20	(70)	64/93	(68.8)	10/16	(62.5)	88/129	(68.2)
Hands: papules and/or vesicles	14/20	(70)	74/93	(79.6)	14/16	(87.5)	102/129	(79.1)
Feet: papules and/or vesicles	17/20	(85)	78/93	(83.9)	10/16	(62.5)	105/129	(81.4)
Buttocks rash ^{##}	16/20	(80)	44/93	(47.3)	3/16	(18.9)	56/129	(43.4)
Outcome (dead)	0	(0)	2/93	(2.2)	0/16	(0)	2/129	(1.6)
ICU survivors	2/20	(10)	2/93	(2.2)	1/16	(6.3)	5/129	(3.9)
Total	20/129	(16)	93/129	(72.1)	16/129	(12)	129	(100)

Includes child-care centres, kindergartens, play schools

Rash includes papules and/or vesicles

TABLE II: VIRUS ISOLATED FROM THE STOOL, THROAT AND SKIN VESICLES OF HFMD PATIENTS AT KKWCH FROM SEPTEMBER TO NOVEMBER 2000

Virus isolated	Stool		Throat		Vesicle		Overall culture	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
EV71	39/63	(61.9)	32/87	(36.8)	13/29	(44.8)	84/96	(87.5)
Coxsackie*	4/63	(6.3)	0/87	(0)	2/29	(6.9)	6/96	(6.3)
EVuntypable	3/63	(4.8)	1/87	(1.1)	0/29	(0)	4/96	(4.2)
Mixed [#]	1/63	(1.6)	1/87	(1.1)	0/29	(0)	2/96	(2.1)
	47/63	(74.6)	34/87	(39.1)	15/29	(51.7)	71/96	(74.0)

* Coxsackie A16, A24, A27, B3, B4

[#] Echo25 or CMV and EV71

23.3 s (12.5-17). The international normalised ratio (INR) and activated partial thromboplastic time (APTT) were within normal limits. However, she remained haemodynamically unstable and tachycardic. She was intubated and ventilated. However, she subsequently developed acute pulmonary oedema needing high ventilatory settings, including FIO₂ of 100%. Her urine output also decreased and she developed hyperkalaemia as well as intractable metabolic acidosis. She remained hypotensive. She died on day 5 of admission and within 6 hours of intubation. Post-mortem findings were that of pulmonary interstitial pneumonitis and moderate pulmonary oedema and there was some evidence of encephalitis and myocarditis, but these were mild compared to the inflammatory features in the lungs. The histopathological features of pneumonitis were suggestive of a viral aetiology. EV71 was isolated from the tonsil, intestine and brain. Viral cultures from the lung, heart, spleen, and oral and tracheal swabs were negative.

The second case was a 29-month-old Chinese boy who was the elder sibling of the first case. He presented with fever and vomiting for 3 days. There were rashes on his hands and feet, and oral ulcers. The result of initial routine haematology revealed a normal total white cell count of $12.7 \times 10^9/L$ (reference range, 5.5-15.5), elevated neutrophil count of $10.54 \times 10^9/L$ (1.5-8.5), lowered lymphocyte of 1.65 (2-8), a slightly low haemoglobin of 11.8 g/dL (12.5-15), normal platelet count of $388 \times 10^9/L$ (150-450). Intravenous fluid and ceftriaxone, and blood pressure monitoring was instituted. A repeat haematology was essentially the same. A routine coagulation profile showed shortened APTT of 26.5 s (27.5-45), with the PT and INR within normal limits. A routine biochemistry showed a slightly lowered sodium of 134 mmol/L (135-145). On the second day of admission, he apparently had a bout of 'coffee-ground' vomitus and became hypotensive. He remained hypotensive despite inotropic support, and also became anuric, and died. The post-mortem findings were that of pulmonary interstitial pneumonitis and moderate pulmonary oedema and there was some evidence of encephalitis with cerebral oedema and myocarditis, but

these were mild compared to the inflammatory features in the lungs. The histopathological features of pneumonitis were suggestive of a viral aetiology. EV71 was isolated from the tonsil and intestine. Viral cultures from the brain, lung, heart, spleen, and oral and tracheal swabs were negative. The cause of haematemesis could be due to stress gastritis, but post-mortem showed stomach and duodenum with normal gastric mucosa with no erosions or ulcers in both the cases.

HFMD-related ICU Admissions

There were another 5 admissions to the ICU.

A 7-year-old boy had mouth ulcers and signs of meningism with headache and vomiting. His lumbar puncture showed a CSF white cell count of 41 cells/mL, protein of 0.56% g/dL, glucose of 3.1 mmol/L, globulin 1+ and his stool was positive for EV71.

An 11-month-old girl had mouth ulcers and a vesicular-papular rash complicated by tachypnoea. Respiratory syncytial virus was positive from nasopharynx by immunofluorescence and EV71 was isolated from mouth ulcers and vesicles.

A 3-year-old girl had mouth ulcers, a vesiculo-papular rash, vomiting, headache and respiratory signs. A chest X-ray revealed a right-sided pneumonia and she was treated with intravenous amoxycillin-clavulanate. EV71 was isolated from vesicle swab and stools.

A 10-month-old male had mouth ulcers a papular rash with vomiting and drowsiness. CT scan of the head was normal, lumbar puncture was not done, and stool and throat cultures did not isolate any viruses.

The 5-year sibling of the 2 children who died was admitted to intensive care unit for close monitoring. He had mouth ulcers, a vesiculo-papular rash over the hands and feet but no fever or vomiting. He was given prophylactic intravenous immunoglobulin 500 mg/kg/day for 3 days. On the third day of illness, he developed acute headache and vomiting. A CT scan of the head was normal; his liver and renal panels were normal; however, his total white cell count climbed from 9,600 to 14,100/dL. The acute headache

and vomiting were diagnosed as benign intracranial hypertension and were attributed to the immunoglobulin infusions, which was stopped. He continued to improve and was discharged 5 days later. His stool isolated EV71 and throat swab isolated CMV suggesting mixed infection. There were no cases of aseptic meningitis or acute flaccid paralysis in our cohort.

By univariate analysis of all factors like age, gender, race, district of residence, attendance to preschool, positive contact history, day of illness to hospital, indication of admission, duration and maximum temperature of fever, presence of vomiting, mouth ulcers, morphology and site of rash, need of intravenous drip, full blood count, serum electrolytes, viral culture from stool, oral and vesicles were analysed for all ICU admissions, including death and stable patients. The factors that were statistically significant were presence of vomiting, rash on hands, raised total white cell count, positive vesicular cultures for virus and abnormal physical examination findings. The districtwise distribution shows 41.3% referral from eastern part of Singapore. This includes (Tampines (14.7%), Bedok, Simei (12.5%), Geylang, Katong, Joo Chiat (7.9%), Pasir Ris (6.2%). This could be due to location of hospital in eastern part of Singapore.

Multiple step-wise logistic regression analysis of the above risk factors for complicated HFMD disease was done and showed no significant relationship for age, sex, duration of fever, morphology of rash, vomiting and type of viruses isolated. A complicated course was associated with mildly raised total white blood cell count of 14,000/dL versus 12,000/dL in uncomplicated patients ($P = 0.04$); however, a white blood cell count of 14,000/dL is still within the normal limit for children less than 10 years old. There was no difference in serum electrolytes of complicated and stable cases. There was no difference in clinical characteristics of EV71 and non-EV71 virus infections.

Discussion

Singapore has a population of 3.893 million spreads over a 659.9m² area. At the time of study, 22.3% of its population were less than 15 years old. The incidence rate of HFMD in children less than 15 years old was 4.06 per 1000 (3526/868,139). The incidence rate of HFMD in KKWCH was 3.7% (129/3526).

Although HFMD is generally a mild and benign illness, it has significant morbidity especially in children less than 5 years old. In this study, children less than 5 years old constituted 87.7% which is similar to the Taiwanese outbreak in 1998 (87%),¹⁰ Gifu, Japanese outbreak in 1978 (87.6%)¹⁴ and Perth Australian outbreak 1986 (85%).¹⁵ This suggests a lower herd immunity for enterovirus in children less than 5 years old. A seroepidemiologic study

done by Ooi et al¹⁶ in Singapore children found the seroconversion rate in children less than 2 years old was minimal. The seroconversion reached a steady state after 5 years old. The geometric mean titre of ant-Human enterovirus antibody declined with age.¹⁶ The male-to-female ratio was 1.3:1 which is similar to the Taiwan,¹⁰ Australian¹⁵ and Japan outbreaks.¹⁴

A similar smaller outbreak was seen in Singapore during the period from 1997 to 1998, in which a total of 527 cases in childcare centres were reported. The attack rate of HFMD was 3.3% to 36.7%. In 1998, a total of 1344 HFMD cases comprising 675 (50.2%) from childcare centres, 669 (49.8%) from government and private clinics and 26 (1.9%) from hospitals were reported.¹⁷ In 1999, 1408 HFMD cases were notified.¹⁷ In April 1997, in Sarawak, Malaysia, 600 cases of HFMD were admitted and over 30 children died. Children that died were frequently critically ill when admitted.^{9,14}

HFMD can be misdiagnosed and sometimes clinically indistinguishable from measles, CMV infection and even Kawasaki disease. Other viruses like CMV can present with macular-papular rash over limbs and be mistaken for HFMD as in our study, in which 2 patients were culture positive for CMV virus from throat swab. Measles can present with fever, papular or macular-papular rash over limbs or body and can also be mistaken for HFMD. During a HFMD outbreak, physicians may tend to over-diagnose children with any rash and fever as HFMD. After the media announcement of HFMD-related deaths in Singapore, more parents were seeking medical attention for any febrile illnesses. However, the combined presence of mouth ulcers, a vesicular or maculopapular rash over palms, soles or buttocks may lead to a clinical diagnosis of HFMD especially during an outbreak. Some of the HFMD patients had concomitant infections with CMV, respiratory syncytial virus, scabies, urinary tract infections and bacterial pneumonia. Therefore, concurrent infection with HFMD should also be considered if the patient has atypical features.

Worldwide, many EV71 outbreaks have been reported since 1975 including 4 other outbreaks with fatalities in young children: Bulgaria, May-September 1975;⁷ Hungary, 1978;⁸ Malaysia, April-June 1997,⁹ Taiwan, 1998.^{6,7} During the peak of the HFMD outbreak, the case fatality rate was 0.085% (3/3526). Other studies have reported case fatality rates of 0.06% (78/129,106).¹⁰ Almost all deaths during the 1975 epidemic in Bulgaria were in infants who were diagnosed to have “bulbar encephalitis” that was initially thought to be due to poliomyelitis.⁷ HFMD, herpangina and pulmonary oedema were not seen during the epidemics in Bulgaria⁷ and Hungary.⁸ The patients who died of encephalomyelitis and pulmonary oedema due to EV71 in the Malaysia epidemic⁹ closely resemble typical patients in

the Taiwan epidemic¹⁰ and our patients who died. The pathogenesis of pulmonary oedema and haemorrhage in EV infection is not well understood. The cause of interstitial pneumonitis is postulated to be due to non-cardiogenic pulmonary oedema. Chang et al¹⁸ suggested that lesions of the spinal cord and medulla disturb the autonomic nervous system and lead to neurogenic pulmonary oedema. No evidence of viral infection was found in the lungs of patients in the Taiwan outbreak. However in our study, the 2 patients who died had interstitial pneumonitis with diffuse haemorrhage, congestion and oedema on post-mortem examinations. Both had mild encephalitis, and myocarditis in 1 case. No enterovirus was isolated from the post-mortem lung biopsy of our patients. This supports the theory of neurogenic pulmonary oedema by Chang et al.¹⁸ Their theory is consistent with the basic neurotropism of enteroviruses and the study of pulmonary oedema in bulbar poliomyelitis.¹⁹ An alternative theory is that of systemic viral sepsis leading to capillary leak syndrome. This possibility could account for metabolic acidosis and hypotension in our patient. Therefore, deaths associated with HFMD may be either in a combination of interstitial pneumonitis, encephalitis or myocarditis.

In the Taiwan outbreak, between April and December 1998, 129,106 cases of HFMD were reported.¹⁰ The viruses isolated were EV71 and Coxsackie A16, similar to our study. In the 1978 outbreak in Gifu, Japan, 75.9% of the patients were positive for EV71. In the Taiwan study, EV71 was most commonly isolated from throat swabs; but in our study, EV71 was most commonly isolated from stool samples. However in Malaysia, EV71 alone was isolated from 19% of patient who died, and adenovirus subgenus B alone or in combination with EV71 was isolated from 66.7% of the children.⁹ Chan et al¹⁸ reported EV71 infection with more severe and serious complications and fatality than illness caused by coxsackie A16 infection. Serious cases occurred in children less than 15 years old and the case fatality was highest between 7 and 12 months old.¹⁰ With the emergence of severe cases of HFMD associated with fatalities in mid-September 2000, the Ministry of the Environment and Ministry of Health made HFMD a legally notifiable disease from 1 October 2000. Surveillance for HFMD at childcare centres, clinics and hospitals was increased. Public health officials from Ministry of the Environment visited childcare centres to observe and reinforce strict hygiene practices for prevention and control of HFMD. The HFMD Task Force convened and ordered all preschools, swimming pools and playgrounds where children were likely to congregate to be closed to children for 2 weeks in order to break the chain of transmission. The number of HFMD notifications drastically diminished in the ensuing weeks.¹¹ It is important to prevent and control

HFMD transmission in view of the fact that no antiviral drugs can cure EV71 and only supportive treatment is available. The potential for antiviral therapy for this family of viruses if available, could significantly impact the clinical course of complicated cases.

Pleconaril is an antiviral broad-spectrum activity against picornaviruses including enterovirus and rhinovirus. This drug is undergoing clinical testing for the treatment of viral meningitis and viral respiratory infections and echovirus 11 has been found to be the most susceptible virus. Pleconaril, however, is not effective against EV71.²⁰ (Personal communications, Viropharma).

The intravenous immunoglobulin (IVIG) has been used prophylactically and therapeutically against enterovirus in neonates and immunocompromised hosts. Its role in severe enterovirus infection is not widely studied.²¹ However, anecdotal case reports have shown a marginal clinical benefit in neonates and some benefits in immunocompromised hosts e.g. HIV infection.^{21,22} The use of IVIG in a single patient in our study was complicated by benign intracranial hypertension. Therefore, the routine use of IVIG is not indicated until more studies defining the role of IVIG are done.

Conclusion

HFMD tends to occur in younger children less than 5 years old suggesting low herd immunity in this age group. Males are more affected than females with male-to-female ratio of 1:3. HFMD is a very infectious disease and had positive contact history in 43% of cases. At least 26% of cases were attending play-school or day-care centre and 43% had positive contact history. This suggests that strict hygiene practices for the prevention and control of the spread of HFMD and surveillance of HFMD at childcare centre and preschools is essential when a HFMD case is diagnosed at any centres. Other viral illnesses e.g. measles, CMV or Kawasaki disease may be mistaken for HFMD in an outbreak setting. EV71 accounted for the majority (75%) of the positive virologic isolations followed by Coxsackie virus. Clinical characteristics of EV71-positive patients show no difference when compared with non-EV71 patients. Enterovirus can cause asymptomatic viral prodrome symptoms to fatal infections causing pneumonitis, encephalitis, and myocarditis. This suggests that clinicians and epidemiologist throughout the world should be aware of the capacity of EV71 to cause large epidemics as well as sporadic cases.

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