Management of Severe Hand, Foot and Mouth Disease in Xiangyang, China from 2008-2013.

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Research

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Abstract

Therapeutic strategies for severe hand, foot and mouth disease (HFMD) are currently either inconsequent or deficient in evidence. We retrospectively surveyed HFMD outbreaks in Xiangyang from June 2008 to December 2013. FHMD is staged form I to V according to clinical severity and the case with central nervous system involvement is defined as a severe one. Most severe cases were investigated to analyse risk factors for fatality and to compare the efficiency and outcome of some therapies by binary logistic regression. The overall HFMD cases included 637 (1.26%) severe cases, 38 fatal cases (0.75‰). Analysis indicates that age (<3 y), enterovirus 71 (+), autonomic nervous system dysregulation, pulmonary edema/hemorrhage, CRP (>40 mg/L) and cardiac troponin I (>0.04 ng/mL) are risk factors for fatality (all $P < 0.05$). Intravenous immunoglobulin (IVIG) and mechanical ventilation applied in early stage IV significantly improved HFMD progression (both $P < 0.05$) with odds ratios of 0.24 (95% CI: 0.10-0.57) and 0.01 (95% CI: 0.00-0.10), respectively. Methylprednisolone and milrinone administered in any stage, and all therapies applied in stage III made no significant difference on mortality (all $P > 0.05$). Precise recognition of the severe HFMD cases in early stage IV and timely IVIG and mechanical ventilation application may decrease mortality. Mechanical ventilation training programs and dispatching specialists to county-level or district hospitals when there is no chance for severe HFMD cases to be transferred to superior hospitals are two key successful administrative initiatives.

Background

Hand, foot and mouth disease (HFMD) is a contagious viral disease caused by more than 20 enteroviruses, including enterovirus 71 (EV71) and coxsackievirus A16 (CA16) [1, 2]. HFMD usually affects infants and children younger than 5 years old. Typical clinical manifestations of HFMD include fever, herpangina and herpes [3] or maculopapular rash on palms, soles, buttocks or limbs. Herpangina or herpes may be present alternatively in a few cases. HFMD with central nervous system (CNS) involvement is defined as a severe case. There is no specific treatment for the disease. Only a minority of severe cases need hospitalization, as a result of uncommon neurological complications such as meningitis, brain stem encephalitis, acute flaccid paralysis or pulmonary oedema/haemorrhage, which can be lethal, particularly to those aged less than 5 years [1–4].

There have been numerous HFMD outbreaks in many cities and provinces in China in recent years [4–10]. HFMD has been categorized as a category C notifiable disease in China since May 2, 2008. The disease is a substantial burden throughout the country. But less is known about what caused the different characteristics of the descriptive epidemiology of HFMD between different areas [5, 7–10], and therapeutic strategies of severe cases are currently either inconsequent or deficient in evidence [11]. Xiangyang was one of the afflicted areas where continuous outbreaks occurred yearly from 2008 to 2013. We retrospectively investigated some epidemiological characteristics of HFMD in Xiangyang, analysed risk factors causing mortality and compared some therapies in this study.

Methods

Study Population and Data Collection

Xiangyang is the second largest city of Hubei Province, China and it administers 3 districts, 3 county-level cities and 3 counties. It has a population of more than 6.0 million people now. The city has a subtropical monsoon continental climate with four well demarcated seasons. Its daily temperature averages from 13 °C in winter to 21 °C in summer and annual mean temperature is 17.0 °C. Rail, highway and airway are very convenient modes of transportation in Xiangyang; thus, the floating population is large in this city.

HFMD cases must be reported to the China Information System for Disease Control and Prevention (CISDCP) after being diagnosed in a clinic. The health authorities in Xiangyang required primary care physicians in villages and communities to register all information of HFMD cases, including who raise the children, the environment and sanitation condition, and to record the manifestation of patients until they are cured. Severe HFMD cases along with their medical records, once diagnosed, must be instantly transferred to one of the three class A tertiary comprehensive hospitals. We collected surveillance data on the prevalence of HFMD in Xiangyang from CISDCP from June 2008 to December 2013, as well as medical records of severe HFMD cases from the three hospitals in the same period. The critical FHMD cases who have lost the chance to be transferred to the three hospitals and the cases died before or in the course of transfer to the three hospitals were also investigated and undertook aetiological detection according to the order from Xiangyang Center for Disease Control and Prevention. We collected variables of all severe and dead cases, such as sex, age, stage of severity on admission, laboratory test results, medicines, ventilation parameters and outcome. Those surviving severe cases had been followed up for sequelae by the end of December 2018.

Clinical Staging of HFMD Cases

HFMD cases are classified into five distinct stages according to clinical severity on admission: stage I refers to cases with fever and eruption on the hands, feet, mouth and buttocks, isolated enanthem or herpangina; stage II refers to those with CNS involvement, such as aseptic meningitis, encephalitis and acute flaccid paralysis. Clinical manifestations include lethargy, sucking weakness, ease of being startled, headache, vomiting, irritability, limb tremors and nuchal rigidity. The above clinical characteristics represent the classic presentation of severe HFMD; stage III refers to those with autonomic nervous system (ANS) dysregulation. Clinical manifestations include resting tachycardia, profuse sweating, cold extremities, and hypertension; stage IV refers to those with tachycardia or bradycardia, hypotension, tachypnea, cyanosis, cough with pink foamy or even bloody sputum indicate frank cardiopulmonary failure, pulmonary oedema or haemorrhage, frequent seizures and severe unconsciousness; and stage V refers to those CNS and cardiopulmonary function gradually recovered, although neurological sequelae may remain in some cases [4].

Sample Preparation and Detection

Serum samples from suspected HFMD cases were drawn for sentinel surveillance to detect IgM antibodies to EV71 with a colloidal gold rapid test kit (WJ-20, Wantai, China), as well as IgM antibody to

CA16 with a diagnostic ELISA kit (WQ-1096, Wantai, China). ELISA test results include all fatal and severe HFMD cases and some cases in stage I, only 10 severe cases including 2 fatal cases were tested in 2008. Additionally, throat and rectal swabs were collected to extract RNA with a Viral RNA Mini Extraction Kit (#52904, Qiagen, Germany), then a OneStep RT-PCR Kit (#210212, Qiagen, Germany) was used followed by electrophoresis to detect EV71, CA16 and general enterovirus for all suspected of severe or fatal HFMD cases after 2008. RT-PCR primers were as follows: enterovirus forward primer 5'- TCC GGC CCC TGA ATG CGG CTA ATC C -3', reverse primer 5'- ACA CGG ACA CCC AAA GTA GTC GGT CC -3'; EV71 forward primer 5'- GCA GCC CAA AAG AAC TTC AC -3', reverse primer 5'- ATT TCA GCA GCT TGG AGT GC -3'; CA16 forward primer 5'-ATT GGT GCT CCC ACT ACA GC-3', reverse primer 5'-TCA GTG TTG GCA GCT GTA GG-3'. Laboratory tests such as blood cell counting, serum glucose, CRP and cardiac troponin I (cTnI) were also performed for severe inpatient HFMD cases.

Treatment Strategies for Severe HFMD Cases

Intravenous immunoglobulin (IVIG) and methylprednisolone were administered to severe HFMD cases as soon as possible after diagnosis. Two different doses, recommended by valid national or provincial HFMD guidelines [4, 12], were selected alternatively according to doctors' favor: IVIG 2 g/kg iv drip singly, or 1 g/kg iv drip, qd for 2 days; methylprednisolone 20 mg/kg iv drip singly, or 1–2 mg/kg iv drip, qd for 2 to 3 days. Milrinone is a positive inotropic cardiotonic agent and vasodilator. Milrinone was administered in cases of persistent resting tachycardia, hypertension or profuse sweating. Milrinone usage was as follows: a loading dose of 25–75 mcg/kg iv, and a maintenance dose of 0.25 to 1.0 mcg/kg per minute. The effects of three injections on mortality were compared between different doses at different stages.

There was no precise recommendation about mechanical ventilation parameters in past few years. Thus, protective-ventilation strategy [13] had been adopted by some doctors. Positive end-expiratory pressure (PEEP) was set at 2–3 cm H_2O above the lower inflection point on the static pressure-volume curve, a tidal volume was set less than 6–8 ml/kg, and peak inspiratory pressure was less than 25 cm H_2O above the PEEP value. Permissive hypercapnia and pressure-limited ventilatory mode were preferred alternative methods. PEEP was set temporarily at 10 cm H_2O above the lower inflection point for 20–40 minutes on pulmonary oedema/haemorrhage at the beginning of mechanical ventilation, when an accidental tube disconnection or extubation, after aspiration of sputum, or in cases when pulmonary oedema/haemorrhage had not been controlled or had reoccurred. In contrast, high-pressure ventilation, including PEEP above 15–20 H_2O and peak inspiratory pressure > 40 cm H_2O, or large-volume control ventilation are characteristics of common ventilation strategy, which was applied by other doctors. Mortalities were compared between protective ventilation and common ventilation strategies.

Statistical Analysis

We analysed the risk factors causing mortality, such as sex, age, stage of severity on admission, blood cell counting, serum glucose, CRP and cTnI by binary logistic regression, and compared the efficiency of different doses of IVIG and methylprednisolone, milrinone and ventilatory strategies on severe HFMD

cases in different stages of severity. The statistical analysis was performed using SPSS Statistics Version 22 (IBM Inc.).

The different choices of medicines and/or doses between patients are derived from differences between national and provincial HFMD management guidelines. All therapies followed national or provincial HFMD management guidelines; therefore, informed consent was waived by the Ethics Committee of Baoan People's Hospital.

Results

Prevalence of HFMD

Epidemiological investigation revealed that the HFMD outbreaks in Xiangyang had gone through four stages in 6 years: a sudden outbreak in 2008, then quick aggravation year by year, a sharp decrease in morbidity after 2012 and then low-level tailing for several years. The HFMD outbreaks involved 50651 cases clinically or laboratorially diagnosed by primary hospitals, of which 637 (1.26%) were severe cases, virologically confirmed by three class A tertiary comprehensive hospitals, and 38 cases were fatal (fatality rate: 0.75‰). It does not rule out that a few severe HFMD have not been transferred to the 3 superior hospitals for having not been precisely recognized or other reasons. A total of 91.14% were 5 years of age or younger, and 74.3% were 3 years of age or younger. EV71 and CA16 were responsible for 58.86% and 16.18% of all cases, 72.53% and 12.45% of the severe cases, and 94.73% and 2.63% of the deaths, respectively. Two peak incidence years had the highest EV71 positive rates: 83.70% in 2011 and 81.60% in 2012. Among the severe cases, male to female ratio was 1.21:1, and the median age was 1.97 years, ranged from 28 days to 9 years. EV71 was found to be the dominating causative virus of HFMD epidemics from 2009 to 2013 (Fig. 1 & Table 1).

Table 1

Virus detection of HFMD in Xiangyang from 2008–2013

Year	All Cases	Severe cases (%)	Fatal cases (‰)	virologically confirmed cases (%)*	EV71 (+) cases (%)	CA16 (+) cases (%)	general enterovirus (+) case (%)
2008	2441	37 (1.52)	2 (0.82)	10 (0.41)	5 (50.00)	1 (10.00)	4 (40.00)
2009	4006	59 (1.47)	3 (0.75)	65 (1.62)	36 (55.38)	14 (21.54)	15 (23.08)
2010	5903	76 (1.29)	6 (1.02)	250 (4.24)	179 (71.60)	32 (12.80)	39 (15.60)
2011	16557	213 (1.29)	18 (1.09)	497 (3.00)	416 (83.70)	45 (9.05)	36 (7.24)
2012	17251	217 (1.26)	8 (0.46)	2668 (15.47)	2177 (81.60)	201 (7.53)	290 (10.87)
2013	4493	35 (0.78)	1 (0.22)	2458 (54.71)	688 (27.99)	706 (28.72)	1064 (43.29)
Total	50651	637 (1.26)	38 (0.75)	5948 (11.74)	3501 (58.86)	999 (16.80)	1448 (24.34)

Abbreviation: EV71, human enterovirus 71. CA16, coxsackievirus A16. *ELISA test results include all fatal and severe cases and some cases in stage I, only 10 severe cases including 2 fatal cases were tested in 2008. Additionally, fatal and all severe cases were confirmed by RT-PCR after 2008.

Table 2

Risk factors analysis on the fatality of severe HFMD cases by binary logistic regression

	Survival number	Death number	P	OR	95% CI
Severe cases	572	38			
Male	388	25	.36		
< 3 years	402	35	.03	9.54	1.20–75.80
ANS dysregulation	276	32	.02	5.77	1.40-23.85
Pulmonary oedema/haemorrhage	73	36	.00	67.59	14.12-323.45
Hyperglycemia	307	29	.38		
EV71(+)	326	36	.00	26.55	3.02-233.04
Leucocytosis (> 13×10^{12}/L)	376	32	.39		
Thrombocytosis (> 500×10^{9}/L)	16	12	.82		
CRP (> 40 mg/L)	73	25	.02	4.74	1.32–16.99
cTnI (> 0.04 ng/mL)	31	29	.00	47.69	11.51-197.57

Abbreviation: ANS, autonomic nervous system; BNP, brain natriuretic peptide; CRP, C-reactive protein; cTnI, cardiac troponin I; OR, odd ratio; CI, confidence interval.

There were two outbreak peaks every year: a higher peak from March to August and a lower peak from October to next January. An investigation shows that EV71 is the main virus that causes serious epidemics, severe morbidity and mortality of HFMD, and the EV71-positive rate of severe HFMD cases decreased coincident with the decrease in HFMD prevalence (Fig. 1 & Table 1).

Analysis on Risk Factors for Fatality

A total of 610 severe HFMD cases including 38 deaths were analysed for fatal risk factors by binary logistic regression, excluding the 27 cases lacking an etiologic diagnosis in 2008 (Table 2). The results indicate that age (< 3 y), EV71 positivity, ANS dysregulation, pulmonary oedema/haemorrhage, CRP (> 40 mg/L) and cTnI (> 0.04 ng/mL) are risk factors for fatality (all $P < 0.05$), but sex, hyperglycemia, leucocytosis (> 13×10^{12}/L) and thrombocytosis (> 500×10^{9}/L) are not at the 5% level. When age was categorized as < 1 y, 1–2 y, 2–3 y and > 3 y, no further significant difference was observed for fatality ($P > 0.05$).

We scrutinized the medical records and phoned the primary care physicians or the patient's parents when the information is incomplete and found that 23.7% of fatal cases, which is much larger than 7.3% of

severe cases, were raised by grandparents ($P < 0.05$). They are too old to be alert, living in remote mountain areas and lacking primary care. Therefore, raising by grandparents is a risk factor of fatality.

Efficiency Comparison between Different Therapies

We compared the efficiency of IVIG, methylprednisolone, milrinone and mechanical ventilatory strategies on severe HFMD in different stages on admission by binary logistic regression (Table 3). The results show that IVIG and mechanical ventilation are significantly relevant to the outcome of severe HFMD in early stage IV (both $P < 0.05$), with odds ratios (ORs) of 0.23 (95% CI: 0.10–0.57) and 0.01 (95% CI: 0.00-0.10), respectively. Protective ventilation did not improve mortality compared with common ventilation strategy ($P > 0.05$). Methylprednisolone and milrinone administered in any stage did not show any significant differences in mortality (all $P > 0.05$). All therapies had no statistical significance regarding outcome in stage III (all $P > 0.05$). No difference in mortality was observed in our data between the large dose and low dose of IVIG or methylprednisolone administered in any stage (all $P > 0.05$).

Table 3
Efficiency comparison between different therapies on HFMD

Treatment and dosage	Survival number	Death number	P	OR	95% CI
In stage II on admission	356	0			
IVIG: L/L/N	139/212/11	0/0/0			
Methylprednisolone: L/L/N	252/98/6	0/0/0			
Mechanical ventilation: Y/N	0/0	0/0			
Milrinone: Y/N	0/0	0/0			
In stage III on admission	170	2			
IVIG: L/L/N	102/68/0	1/1/0	0.76		
Methylprednisolone: L/L/N	134/36/0	2/0/0	0.46		
Mechanical ventilation: Y/N	34/136	0/2	0.48		
Milrinone: Y/N	72/98	1/1	0.83		
In stage IV on admission	73	36			
IVIG: L/L/N	46/27/0	14/16/6	0.00	0.24	0.10–0.57
Methylprednisolone: L/L/N	40/33/0	17/15/4	0.11		
Mechanical ventilation: Y/N	72/1	19/17	0.00	0.01	0.00-0.10
Milrinone: Y/N	34/39	14/22	0.45		
All severe cases	599	38			
Abbreviation: OR, odd ratio; CI, confidence interval; IVIG, intravenous immunoglobulin; L/L/N, large dose/low dose/none; Y/N, yes/none.					

Our investigation found that 78% of fatal cases before 2011 occurred on the way to or within 12 hours after transfer to a superior hospital, which was attributed largely to a delay in applying mechanical ventilation.

Prognosis Follow-up

Primary care physicians in villages and communities were asked to supervise the discharged HFMD cases. Those cases remaining or newly emerging any neurological symptoms after discharge were ordered to return monthly to the pediatric neurology clinic of the three class A tertiary hospitals. Eighteen children have been followed-up by the end of December 2018. Our investigation showed that 4 patients with acute flaccid paralysis and 3 other ones with unilateral abducens nerve paralysis had recovered

within 2 to 5 months without further intervention, and no central nerve system sequelae or any complications were found for surviving patients who had received a large dose of methylprednisolone.

Discussion

Our investigation reveals that elevated CRP and cTnI levels have been shown to be useful laboratory markers to identify severe HFMD cases at risk of systemic complications several hours before the onset of overt signs of deterioration. Hyperglycemia and leucocytosis are not risk factors for poor prognosis, which is inconsistent with the report from Hainan, China [14]. Another study identified that being female and having light-reflex insensitivity, tachycardia and high serum lactate levels are independent risk factors, and longer onset-to-hospitalization time is an independent protective factor for death in children with critical and severe HFMD [15].

Our investigation suggests that immediate IVIG and mechanical ventilation application to severe HFMD in early stage IV may improve pulmonary oedema or haemorrhage and mortality. A protective-ventilation strategy might outweigh common ventilation strategies in maintaining normal blood pressure, but no mortality difference between ventilation strategies was found. High airway pressure and PEEP may have extrapulmonary effects such as reducing the volume of venous return, increasing the afterload in the right atrium, decreasing cardiac output, decreasing visceral venous return, impairing renal function, and altering hormonal levels [13]. PIP and PEEP should be regulated according to the lower inflection point and upper inflection point on the static pressure-volume curve.

We found milrinone is effective in reducing hypertension and sympathetic tachycardia, and methylprednisolone can accurately decrease high body temperature, which has been proven by many cases, but neither of them contributed significantly to the survival rate in our data. In contrast, a study in Taiwan (China) found that a milrinone-treated group was associated with reduced mortality corresponding to attenuated sympathetic activity and cytokine production in comparison with a non-treated group [16]. IVIG and methylprednisolone have been used in many countries and districts on a presumptive basis and have been shown to improve symptoms and decrease inflammatory factor storm for severe HFMD [17, 18]. Elevated serum levels of inflammatory cytokines, including IL-3, IL-6, IL-12p40 and TNF-α, and decreased levels of serum biomarkers, including IL-1Ra, IL-8, IL-16, soluble ICAM-1, CXCL-1 and CCL27, were found in HFMD cases, which suggests that systemic inflammation is involved in the aetiology of HFMD. In contrast, the associated biomarkers did not make any difference in the patients treated with methylprednisolone [19], and methylprednisolone was even associated with an increased risk of severe HFMD development [20]. Therefore, further investigations are needed to determine the usefulness of steroid treatment for HFMD.

We also found that there is not enough evidence to suggest large dose of IVIG instead of low dose one in any stage, and that no sufficient evidence hasten the application of mechanical ventilation or IVIG on HFMD in stages II or III.

We realize that it usually takes several hours for severe HFMD to deteriorate from stage III to stage IV, but there is usually less than one hour to take quick action after it get into stage IV. Severe cases should thus

be closely monitored for signs indicative of CNS involvement, ANS dysregulation and the development of cardiopulmonary failure, and timely intervention or even mechanical ventilation is the key to reducing mortality associated with severe HFMD. Persistent high fever, vomiting, lethargy, agitation and irritability are indications of CNS involvement [21, 22]. More specific neurological signs, such as myoclonic jerk (usually observed during the early stage of sleep but also seen in severe cases when patients are awake), truncal ataxia and “wandering eyes” (rotary eye movement without fixation), are commonly observed in severe pediatric cases [23]. With disease progression or increased severity affecting the ANS and leading to cardiopulmonary failure, signs such as mottled skin and dyspnoea/tachypnoea may also be evident in stage IV. We found that patients raised by grandparents is a risk factor for fatality, which is due to a delay in the early recognition of severe cases and a loss of timely intervention.

Fatal cases of HFMD are the most common cause of medical disputes and medical compensation in China in recent years, which is the consensus of many pediatricians and lawyers in medical litigation. There is lots of related news on the internet. When our survey shows that unsuitable transfer of deteriorated patients may result in an increase in mortality and medical disputes, the health authorities quickly equipped all paediatric departments with mechanical ventilators for all county-level and district hospitals and emphasized early recognition of severe cases and compliance with indication and contraindication to transfer and held comprehensive training sessions on mechanical ventilation management. Specialists were dispatched to county-level or district hospitals when there was no chance for severe HFMD cases to be transferred to superior hospitals. HFMD fatalities had decreased significantly since new policies were enforced after 2011.

It is puzzling that the outbreaks of HFMD were so severe in Xiangyang for several years, whereas adjacent areas were less impacted, and severe morbidity and mortality among districts, county-level cities and counties were very different in Xiangyang. A study in Shandong Province, China, also showed spatiotemporal differences in HFMD prevalence [24]. We cannot convincingly interpret the difference as the result of climate, bad environment, insalubrity, large floating population and/or poor education. There were no fatal cases in stage II and only 2 fatal cases in stage III on admission in our data. When more severe cases and fatalities are enrolled and a randomized, double-blind, placebo-controlled trial design is adopted, we presume that the efficiency of IVIG and methylprednisolone administration in stages II or III may improve and that stage IV may be held at bay. Future studies also need to be performed to understand why these outbreaks occur and why some people have severe cases.

Conclusions

The precise recognition of severe HFMD cases and timely IVIG and mechanical ventilation application in early stage IV can significantly decrease mortality. Mechanical ventilation training programmes and dispatching specialists to county-level or district hospitals when there is no chance for severe HFMD cases to be transferred to superior hospitals are two key successful administrative initiatives.

Abbreviations

ANS:autonomic nervous system; CI:confidence interval; CNS:central nervous system; CA16:coxsackievirus A16; cTnI:cardiac troponin I; EV71:human enterovirus 71; HFMD:hand, foot and mouth disease; PEEP:Positive end-expiratory pressure; IVIG:intravenous immunoglobulin; MAP:mean airway pressure; OR:odds ratio.

Declarations

-Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of Shenzhen Baoan People's Hospital (BYL20190401). It is a retrospective investigation, and all therapies followed national or provincial HFMD management guidelines; therefore, informed consent has been waived by the Ethics Committee.

- Consent to publication

Not applicable.

- Availability of data and material

The data can be shared when emailing the corresponding author Dr Jian L.

- Competing interests

All authors declare that they have no conflict of interest.

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- Authors' contributions

Jian L designed the study. Jing Q was responsible for following up the neurological sequelae of severe cases. Jian L and Jing Q collected and analysed data, drafted and revised the manuscript. All authors read and approved the manuscript.

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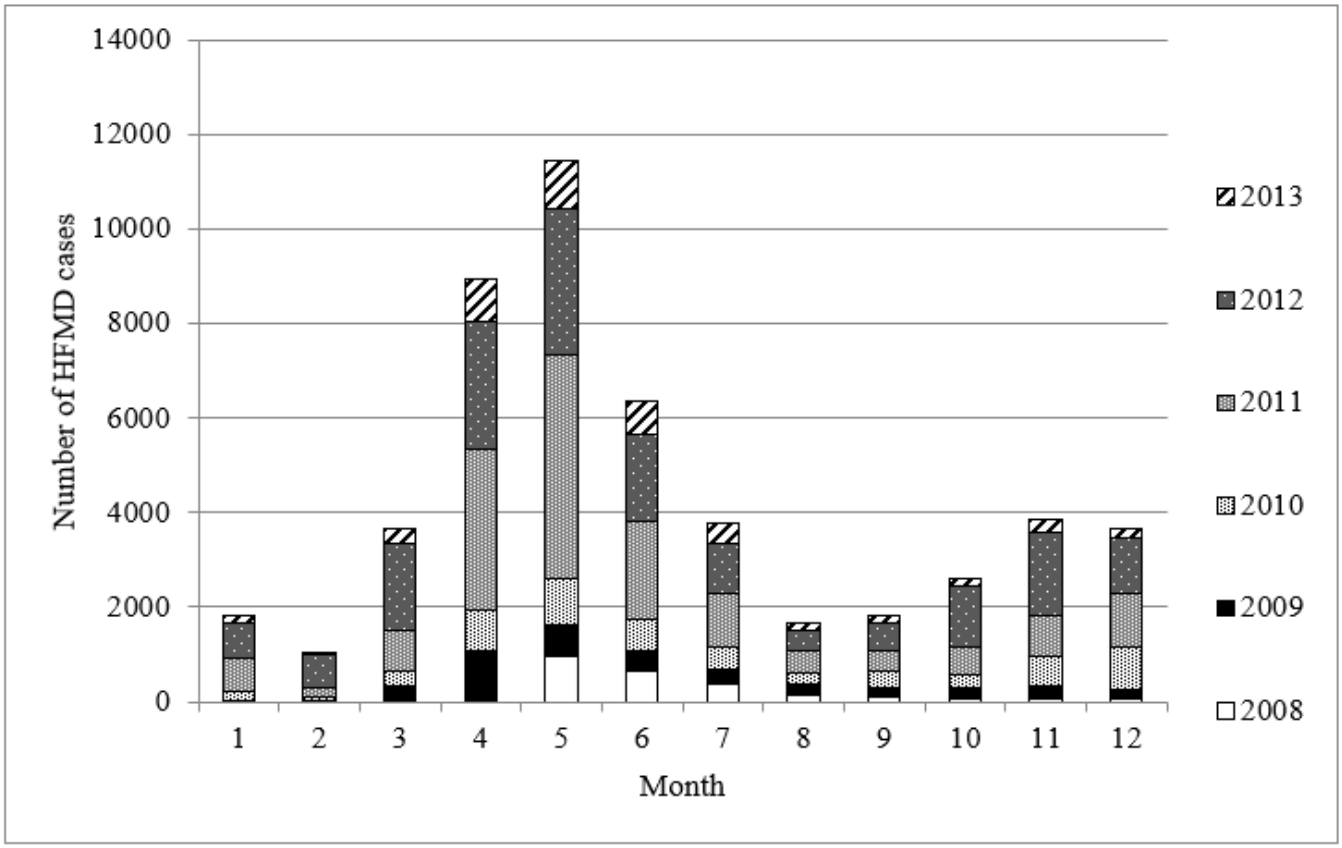
References

1. Ventarola D, Bordone L, Silverberg N. Update on hand-foot-and-mouth disease. Clin Dermatol. 2015;33(3):340-6. doi: 10.1016/j.clindermatol.2014.12.011.
2. Ooi MH, Wong SC, Lewthwaite P, Cardosa MJ, Solomon T. Clinical features, diagnosis, and management of enterovirus 71. Lancet Neurol. 2010;9(11):1097-105. doi: 10.1016/S1474-4422(10)70209-X.
3. Solomon T, Lewthwaite P, Perera D, Cardosa MJ, McMinn P, Ooi MH. Virology, epidemiology, pathogenesis, and control of enterovirus 71. Lancet Infect Dis. 2010;10(11):778-90. doi: 10.1016/S1473-3099(10)70194-8.
4. Li XW, Ni X, Qian SY, Wang Q, Jiang RM, et al. Chinese guidelines for the diagnosis and treatment of hand, foot and mouth disease (2018 edition). World J Pediatr. 2018;14(5):437-47. doi: 10.1007/s12519-018-0189-8.
5. Liang YK, Li N, Yang JZ, Deng B, Xie RH, Shu S, et al. Epidemiologic characteristics of hand-foot-mouth disease in Guiyang between 2008 and 2010. Zhongguo Dang Dai Er Ke Za Zhi. 2012;14(3):195-7.
6. Lee MK, Chan PK, Ho II, Lai WM. Enterovirus infection among patients admitted to hospital in Hong Kong in 2010: Epidemiology, clinical characteristics, and importance of molecular diagnosis. Journal of Medical Virology. 2013; 85(10):1811-7.
7. Xing W, Liao Q, Viboud C, Zhang J, Sun J, Wu JT, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. The Lancet. Infectious Diseases.2014;14(4):308-18.
8. Sun LM, Wu SL, Tan XH, Li H, Yang F, Zeng HR, et al. Epidemiological characteristics of Coxsackie virus A16 caused hand foot and mouth disease cases in Guangdong province, 2012-2016. Zhonghua Liu Xing Bing Xue Za Zhi. 2018;39(3):342-6.
9. Li Y, Bao H, Zhang X, Zhai M, Bao X, Wang D, et al. Epidemiological and genetic analysis concerning the non-enterovirus 71 and non-coxsackievirus A16 causative agents related to hand, foot and mouth disease in Anyang city, Henan Province, China, from 2011 to 2015. Journal of Medical Virology. 2017;89(10):1749-58.
10. Chen Q, Xing XS, Wu Y, Liao QH, Liu GP, Jiang XQ, et al. Hand, foot and mouth disease in Hubei province, 2009-2015: an epidemiological and etiological study. Zhonghua Liu Xing Bing Xue Za Zhi. 2017;38(4):441-5.
11. Qian SY, Li XW. Epidemiology and management development of hand-foot-and-mouth disease in Chinese mainland: a ten-year review. Zhonghua Er Ke Za Zhi. 2018;56(5):321-3.
12. Clinical Experts Group of the Ministry of Health for Hand, Foot and Mouth Disease. Experts consensus on rescue and treatment of severe cases with enterovirus 71 (EV71) infection. Zhonghua Er Ke Za Zhi. 2011;49(9):675-8.
13. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. The New England journal of medicine. 1998; 338:347-54.

14. Liu RH, Li J, Qu XF, Xu YJ, Qu NY, Feng XC. Clinical characteristics and prognostic factors of children with critical hand-foot-mouth disease treated with mechanical ventilation. Zhongguo Dang Dai Er Ke Za Zhi. 2015; 17:249-53.
15. Zheng G, Cao J, Yu J, Zhang Z, Liu Q, Chen J. Risk factors for death in children with critical and severe hand-foot-and-mouth disease in Chongqing, China: An observational study. Medicine (Baltimore). 2017; 96:e8934.
16. Wang SM, Lei HY, Huang MC, Wu JM, Chen CT, Wang JN, et al. Therapeutic efficacy of milrinone in the management of enterovirus 71-induced pulmonary edema. Pediatric Pulmonology. 2005; 39(3):219–23.
17. Jiang M, Wang XC. Clinical research of early, enough methylprednisone combined with immunoglobulin in treatment of severe hand-foot-mouth disease. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi.2013;27(5):363-5.
18. Wang SM, Lei HY, Huang MC, Su LY, Lin HC, Yu CK, et al. Modulation of cytokine production by intravenous immunoglobulin in patients with enterovirus 71-associated brainstem encephalitis. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2006; 37:47-52.
19. Zeng M, Zheng X, Wei R, Zhang N, Zhu K, Xu B, et al. The cytokine and chemokine profiles in patients with hand, foot and mouth disease of different severities in Shanghai, China, 2010. PLoS neglected tropical diseases. 2013; 7:e2599.
20. He Y, Yang J, Zeng G, Shen T, Fontaine RE, Zhang L, et al. Risk factors for critical disease and death from hand, foot and mouth disease. The Pediatric infectious disease journal. 2014; 33:966-70.
21. Ooi MH, Wong SC, Mohan A, Podin Y, Perera D, Clear D, et al. Identification and validation of clinical predictors for the risk of neurological involvement in children with hand, foot, and mouth disease in Sarawak. BMC Infectious Diseases. 2009; 9:3.
22. Wang SM, Liu CC, Tseng HW, Wang JR, Huang CC, Chen YJ, et al. Clinical spectrum of enterovirus 71 infection in children in southern Taiwan, with an emphasis on neurological complications. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 1999; 29:184-90.
23. Lu HK, Lin TY, Hsia SH, Chiu CH, Huang YC, Tsao KC, et al. Prognostic implications of myoclonic jerk in children with enterovirus infection. Journal of microbiology, immunology, and infection. 2004; 37:82-7.
24. Li L, Qiu W, Xu C, Wang J. A spatiotemporal mixed model to assess the influence of environmental and socioeconomic factors on the incidence of hand, foot and mouth disease. BMC Public Health. 2018; 18:274.

Figures

Figure 1 The prevalence of HFMD in Xiangyang, China from 2008-2013



Abbreviation: HFMD, hand, foot and mouth disease. There were two outbreak peaks every year: a higher peak from March to August and a lower peak from October to next January. 2011 and 2012 were the worst two years.

Figure 2

The prevalence of HFMD in Xiangyang, China from 2008-2013 Abbreviation: HFMD, hand, foot and mouth disease. There were two outbreak peaks every year: a higher peak from March to August and a lower peak from October to next January. 2011 and 2012 were the worst two years.