Original Article

Characterization of Hand, Foot, and Mouth Disease in China between 2008 and 2009

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Abstract

Objective To investigate the epidemiological and clinical features of hand, foot and mouth disease (HFMD) since several outbreaks of HFMD caused by enteroviruses were documented in China between 2007 and 2008.

Methods HFMD cases reported to the National Infectious Disease Information Management System database between May 2008 and April 2009 were assessed. Clinical features in some of the severe and fatal cases were analyzed the etiology of the outbreaks was investigated.

Results 89.1% of reported HFMD cases were found in children<5 year-old with an age-specific incidence rate of 834.1/100 000 in the first year as the notifiable disease in China from May 2008 to April 2009. The incidence, mortality and percentage of severe cases were studied for three regions of China and found to be highest in the central region. The incidence of severe cases and mortality in rural population were significantly higher than those in urban population. Among the laboratory confirmed EV17 positive cases there were 52.6% mild, 83.5% severe, and 96.1% fatal cases. More myoclonic jerks were found in the severe case group than in group that died. Tachypnea, lip purpling, pink foaming and low limb temperature occurred more frequently in the fatal cases than in the severe cases.

Conclusion The epidemic of HFMD in China was characterized predominantly by EV71 infections, had relatively high mortality rates especially in the central region, and was most prevalent in young, rural populations.

Key words: Hand, foot, and mouth disease; Enterovirus; Epidemiology; Clinical features

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INTRODUCTION

Human enterovirus 71 (EV71) was first isolated from a child who died from encephalitis in the United States in 1969[1]. Since 1997, outbreaks or epidemics of hand, foot and mouth disease (HFMD) associated with EV71 infections have occurred in the Asia Pacific region[2-4]. In 1998, a large EV71 outbreak in Taiwan caused 129 106 HFMD or herpetic angina cases, with 405 severe infections and 78 deaths[5]. In mainland China, the EV71 strain was first isolated from a case of HFMD without neurological symptoms in 1987[6]. In April 2007, an EV71 outbreak resulting in 14 deaths occurred in Linyi City of Shandong province in China. In 2008, 23 deaths from HFMD in Fuyang City of Anhui province in China were confirmed as EV71 infection[7-8]. The clinical features of cases of mortality in Shandong and Anhui provinces were

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similar, with acute onset and severe pneumonia, from which the victims usually died rapidly of cardio-respiratory arrest. To control the HFMD infections and decrease mortality from HFMD in mainland China, the Chinese Ministry of Health listed HFMD as a notifiable disease in mainland China on May 2nd, 2008. Based on the first year's surveillance data from May 2008 to April 2009, we conducted this study to establish the epidemiological characteristics, etiology and clinical features of the HFMD and to design control measures for mainland China.

MATERIALS AND METHODS

Case Reporting

The Chinese Law of Infectious Disease Prevention and Control declared HFMD a notifiable infectious disease in May 2008 and the HFMD case-reporting criteria were defined by the Chinese Ministry of Health[9]. Infection data were reported to the China CDC's database of National Infectious Disease Information Management System.

The case definition of HFMD includes mild and severe cases. The mild cases were defined by the presence or absence of fever with a rash on the buttocks of papula or herpetic lesions. The severe cases were defined by infection accompanied by neurological complications (including vomiting, limb twitching, encephalitis or meningitis), respiratory dysfunction (lung edema, pink bubble phlegm, and dysfunction, including increases in peripheral blood leukocyte count and hyperglycemia.

Laboratory diagnosis was established by one of the following tests: (1) amplification of nucleic acid of CoxA16, EV71 or other enteroviruses causing HFMD; (2) virus isolation; (3) detection of neutralizing antibodies of EV71, CoxA16 or other viruses causing HFMD[9].

Laboratory Surveillance

Hospital and local CDC personnel were responsible for collecting case samples, including throat swabs, stool samples, cerebrospinal fluid, and in some cases, blood samples. The hospital staff and local CDC personnel collected specimens from a sample of five mild cases from each county every month. Samples were obtained from all severe and fatal cases. All samples were sent to provincial CDC and part of prefecture CDC laboratories for real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) testing and virus isolation using established methods[9].

Clinical Investigations in Eight Provinces

The China CDC conducted an investigation of severe and fatal cases in Henan, Fujian, Heilongjiang, Liaoning, Hunan, Neimenggu, Zhejiang, and Shanxi provinces between 2008 and 2009. A questionnaire was used to collect information regarding clinical manifestations associated with the severe and fatal HFMD cases.

Data Analysis

The incidence rate and percentage of severe cases in each group were compared using the Poisson regression or logistic-regression analysis. Pearson's correlation and multiple liner regression were used in the analysis of risk factors associated with incidence and fatality rate. A p value of less than 0.05 was considered to indicate statistical significance. All analyses were carried out using SPSS (Statistical Package for Social Sciences, Chicago, IL) version 17.0.

RESULTS

HFMD was categorized as the notifiable infectious disease in China on May 2nd, 2008 and the first year's surveillance data from May 2008 to April 2009 were collected and analyzed. There were 765 220 cases reported with an incidence rate of 57.9/100 000 (Table 1). The data demonstrated a wide spectrum of clinical HFMD disease with about 99% mild cases and 1% severe cases with 5% death among the severe cases. There were 205 fatal cases and 4 067 severe cases reported. About 2.2% cases were confirmed by laboratory testing and EV71 positive cases accounted for 56.1% of all the laboratory confirmed cases. Among the laboratory confirmed mild, severe and fatal cases, there were 52.6%, 83.5%, and 96.1% EV71 positive cases respectively. EV71 was the predominant strain found in the epidemic of HFMD in China between May 2008 and April 2009.

Geographic Distribution

All 31 provinces of mainland China reported HFMD cases. Of the 205 deaths reported, 74.2% were laboratory confirmed cases and 92.7% were from rural areas (Table 1). Among the severe cases reported, 91.5% were from rural areas and 40.7% were laboratory confirmed. The incidence rate (0.5/100 000) and mortality rate (0.03/100 000) of severe cases in rural areas were significantly higher

than the rates in urban areas (0.07/100 000 and 0.003/100 000) (P<0.01). The incidence rate of severe cases and mortality rate in rural area of the central region were higher than the rates in the other two regions.

Three regions in China were categorized by geographical location (latitude/longitude) as follows: (1) the southern region consisting of provinces located 30 degrees south of the Yangtze River and including Guangdong, Guangxi, Hainan, Fujian, Zhejiang, Shanghai, Jiangsu, Anhui, Jiangxi, Hunan, Hubei, Chongqing, Sichuan, Yunnan, and Guizhou provinces (n=15), (2) the central region consisting of most provinces located between 30-40 degrees north latitude north of the Yangtze river including Henan, Hebei, Shanxi, Tianjin, Beijing, Shanxi, and Shandong provinces (n=7) and (3) the northern region, was located 40 degrees north latitude and west of the 105 longitude line and included regions of higher elevation such as Xinjiang, Gansu, Ningxia, Neimenggu, Qinghai, Xizang, Liaoning, Jilin, and Heilongjiang provinces (n=9).

Table 1. Comparison of HFMD Incidence, Mortality and Laboratory Results in Different Regions

Disease Index	Total	Southern Region (A)	Central Region (B)	North Region (C)
Number of cases reported	765 220	436 103	261 159	67 958
No. of deaths	205	102	93	10
Number of severe cases	4 067	1 068	2 929	70
Incidence rate (1/100 000)‡	57.9	58.2	73.4	35.0
Mortality rate (1/100 000)‡	0.03	0.01	0.03	0.005
Case fatality rate (%)‡	0.03	0.023	0.04	0.02
Percentage of severe cases (%)‡	0.5	0.2	1.1	0.1
Percentage of deaths among severe cases (%)‡	4.8	8.7	3.1	12.5
Percentage of severe cases of rural area (%)‡	91.5	88.8	92.8	78.6
Percentage of deaths of rural area (%)	92.7	90.2	97.9	70.0
Incidence of severe cases of rural areas (1/100 000)‡	0.5†	0.2	1.4	0.07
Incidence of severe cases of urban areas (1/100 000)‡	0.07†	0.04	0.2	0.02
Mortality in rural areas (1/100 000)‡	0.03†	0.02	0.05	0.007
Mortality in urban areas (1/100 000)‡	0.003†	0.004	0.002	0.004
Number of lab confirmed cases	16 513	8 516	6 308	1 689
Number of EV71 positive cases	9 271	4 552	3 930	789
Number of CoxA16 positive cases	3 367	2 000	750	617
Number of other EV positive cases	3 875	1 964	1 628	283
Percentage of EV71 lab confirmed cases (%)‡	56.1	53.4	62.3	46.7
Percentage of CoxA16 lab confirmed cases (%)‡	20.4	23.4	11.9	36.5

Note. ‡A and C group, B and C group were compared and all P value <0.05; †Rural and urban incidence or mortality in the total group were compared and all P value <0.05.

The HFMD incidence, mortality and the percentage of severe cases among southern, central and northern regions of China are described in Table 1. For all the variables measured, significant differences were found among the three regions. The incidence, mortality, and percentage of severe cases and the percentage of EV71 infections (confirmed by laboratory tests) were highest in the central region and lowest in the northern region; while mortality, the percentage of severe cases and the percentage of CoxA16 infections were lowest in the central region (P<0.01). However, the highest percentage of deaths among the severe cases (12.5%) was observed in the northern region (P<0.01). The morbidity and the mortality patterns of HFMD were found to be associated with the different geographic locations, indicating that the epidemic risk in three regions varied.

Seasonal Distribution

A large spring peak of HFMD occurred between April and May with a second smaller peak in October

in the central and southern regions. A single peak was observed in the northern region in July, two months after the first peak observed in the central and southern regions (Figure 1).

The incidence, case fatality rate and EV71 positive infections in the central region increased gradually from May 2008 to April 2009 and were all higher than those in the southern and northern areas. In the southern region, the incidence, case fatality rate and EV71 positive infection rate in May 2008 was the highest between the three regions, but decreased gradually from June to December 2008, and in March 2009 began to rise again but to a lower level than that in the central region (Figure 2 and Figure 3). In October 2008, the smaller epidemic peak in the southern region was clear, reflecting the increasing EV71 infections. In the northern region, however, no peak in EV71 infections was observed.

In March at the beginning of the HFMD epidemic, there was a higher proportion of death among the severe cases in some counties in the central region (5%-13%). In the May-June peak periods, the proportion of deaths in severe cases decreased sharply to 2%-3%.

Population Distribution

HFMD cases were observed primarily in children <15 years old (99.6%) with an age-specific incidence rate of 308.6/100 000. 98.6% of cases were under 10 years old, and 89.1% cases were observed in children <5 years of age with an age-specific incidence rate of 834.1/100 000. The highest age-specific incidence rate (1204.6/100 000) was observed in 2-year-old children. The highest mortality rate (0.6/100 000), case fatality (0.06%) and percentage of severe cases (1.0%) were observed in 1-year-old children (Figure 4). The percentage of severe cases among the 7 years old children (0.3%) had a smaller rise than those among the 6.year old (0.2%) and 8 years old children (0.2%).

The overall age-range of mild, severe and fatal cases was from 28 days to 80 years, 2 months to 17 years, and 2 months to 5 years of age, respectively. The percentage of children who stayed at home and the percentage of children in kindergarten were 66.4% and 28.1%, respectively. The male to female ratio in mild, severe and fatal cases were 17, 20, and 19, respectively.

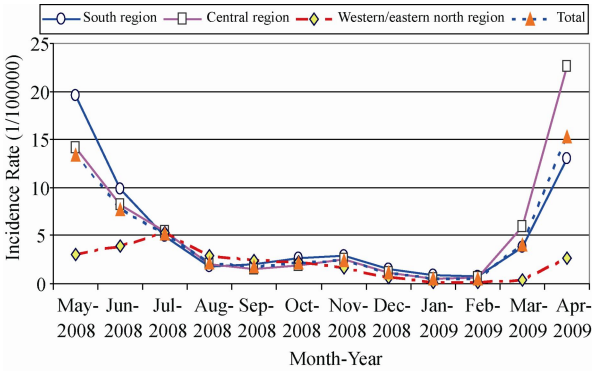

Figure 1. Incidence rate of HFMD in different regions.

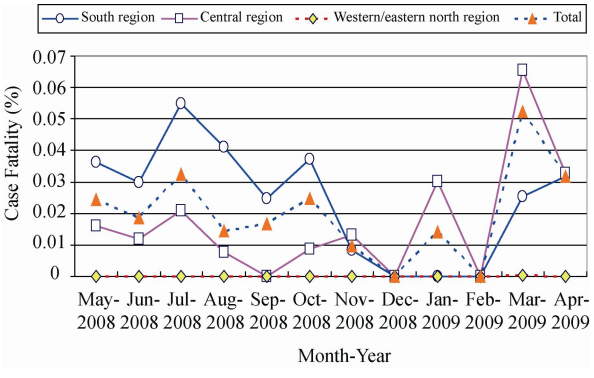

Figure 2. Case fatality rate of HFMD in different regions.

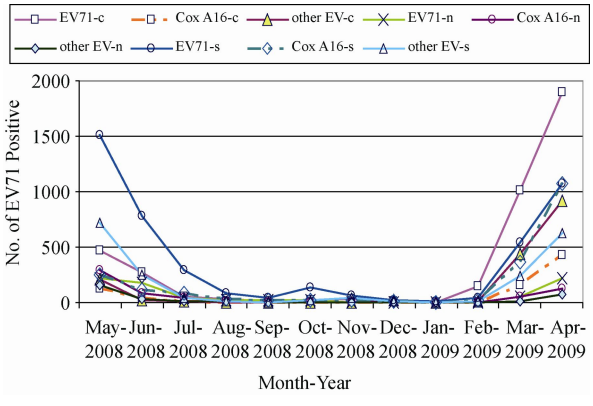

Figure 3. Number of enterovirus positive cases in three regions.

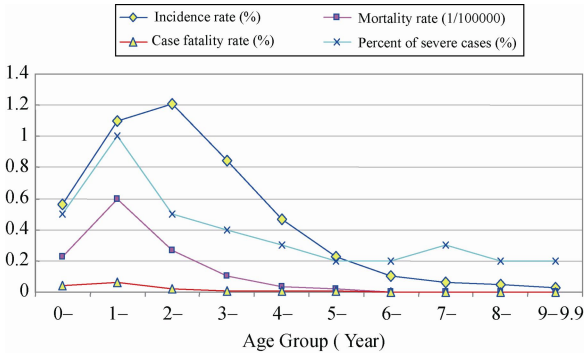

Figure 4. Distribution of morbidity, mortality of HFMD in children <10 years old.

Etiology and clinical features

Total of 1 658 lab confirmed severe cases were reported with 36.0% lab confirmed percentage in severe case group. In fatal case group, there were 152 lab confirmed cases with 74.1% lab confirmed percentage. The percentages of EV71 positive infections resulting in severe (72.4%-100%) and fatal cases (86.2%-100%) between different age groups were similar. All fatal cases due to EV71 were found exclusively in young children ⩽5 years old.

The percentage of EV71 infections in fatal cases was significantly higher than the percentage of cases observed in either mild (OR: 21.9, 95% CI: 9.1 to 49.7, P<0.001) or severe cases (OR: 4.6, 95% CI: 4.0 to 5.2, P<0.001). In contrast, the percentage of CoxA16 positive infections was significantly associated with mild cases rather than fatal cases (OR: 44.1, 95% CI: 6.2 to 315.4, P<0.001). In severe cases, however, there was no significant difference between CoxA16 and EV71 infections (P<0.05). EV71 gene sequencing of isolates identified from mild, severe and fatal cases revealed that all viruses belonged to the genotype C4. Only one fatality was attributed to a CoxA16 infection (Table 2).

Table 2. Comparison of Enterovirus Positive Percentage and Clinical Features between Severe Case and Fatal Case of HFMD

Characters	Severe Case Group *n* (%)	Fatal Case Group *n* (%)	χ^2	*P* value
Total of lab confirmed cases	1658(36.0)	152(74.1)		
EV71 positive cases	1384 (83.5)	146 (96.1)	15.9	0.000
CA16 positive cases	37 (2.2)	1 (0.7)	1.4	0.237
Total of clinical investigated cases	158	31		
Fever	145(96.0)	30 (96.4)	2.6	0.272
⩾38°C	111 (91.0)	24 (92.3)	0.05	0.826
Skin rash	147 (97.4)	27 (96.4)	1.3	0.527
Headache	19 (19.2)	2 (8.3)	2.3	0.133
Myoclonic jerks	42 (43.8)	5 (20.0)	4.7	0.030
Limb weakness	18 (18.6)	6 (22.2)	0.2	0.670
Limb paralysis	3 (3.3)	0 (0)	1.4	0.235
Lethargy	7 (7.9)	2 (9.1)	0.04	0.852
Coughing	34 (32.4)	9 (36.0)	0.1	0.730
Pharyngalgia	23 (23.5)	3 (12.5)	1.4	0.240
Tachypnea	25 (26.3)	12 (50.0)	5.0	0.025
Lip purpling	7 (19.1)	11 (45.8)	17.0	0.000
Pink foaming at the mouth	4 (4.9)	13(56.5)	31.6	0.000
Rapid heart rate	36 (37.5)	13 (50.0)	1.3	0.249
Low limb temperature	7 (7.7)	10 (40.0)	13.7	0.000
Diarrhea	8 (8.8)	5 (20.0)	2.2	0.139

Clinical data associated with 158 severe cases and 31 fatal cases were collected from HFMD-assigned hospitals in eight provinces. Because mild cases were simply defined as rash or ulcer involvement, we only compared the clinical characters between severe and fatal cases. In severe cases, the proportion of myoclonic jerks with central nervous system involvement was significantly higher than that observed in fatal cases (χ^2=4.7, P<0.05), but the respiratory and circulatory system involvement manifestations (lip purpling, pink foaming at mouth, low limb temperature) were significantly higher in fatal cases (Table 2). The median time from onset to death was 3 days. The percentages of fever and skin rash were higher in both severe and fatal cases.

Risk Factors for HFMD Epidemics

The data from 31 provinces were used to identify potential risk factors. Bivariate correlations were performed to compare incidence of severe and fatal infections with several factors, including total population and population density, rural versus urban living, literacy, climate (average yearly temperature, rainfall and hours of sunshine in 2008), and enterovirus positivity. Significant Pearson's correlation coefficients are listed in Table 3. In general, the climatic factors were correlated with incidence and mortality. The severe cases and fatal cases of HFMD were associated with rural population, under 6 years of age and with level of medical care.

Multiple linear regression analysis was used to identify common disease risk factors. Based on the results in Table 3, we selected six dependent variables, including number of cases, severe cases, fatal cases, incidence rate, case fatality rate, and percentage of severe cases. Nine independent variables were selected, including population, population under 15 years old, population under 6 years old, rural population, population density, average annual temperature, humidity, sunlight hours, and average rainfall in 2008, and participation of farmers in new rural cooperative medical care in 2008. A stepwise comparison method was used, and the results showed that two multiple liner regression models were established through significant statistic testing (see Model 1 and Model 2).

The multiple liner models using number of severe cases, deaths, case fatality rate or percentages of severe cases are not shown because the models were not statistically significant. Model 1 indicated that the population density, average annual temperature and sunlight hours were potential contributory factors for the incidence of HFMD. In Model 2, the rural population and population density were related to the number of severe cases, but the humidity was negatively associated with number of severe cases. Based on the R^2_{adjust} of models, two multiple liner models can partially explain the impact on the incidence rate and the number of severe cases of HFMD which were 52% and 53%, respectively.

Model 1:

Incidence=–66.66 + 0.03 population density + 4.41 temperature +0.024 sunlight Hours

R^2_{adjust}-1 = 0.52

Model 2:

Number of severe cases=467.88+0.16 rural population-11.79 humidity+0.15 population density

R^2_{adjust}-2 = 0.53

Table 3. Pearson Correlation Coefficients among Disease Indexes and Potential Determining Factors of HFMD

Order	Index name	Potential determine factors of HFMD							
		Population	Population <15years	Population <6 years	Rural population	Population density	Year average temperature of 2008	Year average rainfall of 2008	Participants of new rural cooperative medical care
1	No. of cases		0.769	0.845	0.730		0.479		
2	No. of fatal cases		0.764	0.721	0.693		0.401		
3	No. of severe cases		0.597	0.600	0.631				
4	Incidence					0.617	0.478	0.361	
5	Case Fatality		0.452		0.379		0.415	0.413	0.386
6	Percent of severe cases	0.472	0.477	0.464	0.507				0.528
7	No. of EV71 positive		0.547	0.550	0.526				
8	No. of CoxA16 positive		0.502	0.534				0.315	
9	No. of other EV		0.560	0.556	0.481				

DISCUSSION

We have analyzed the disease characteristics and the risk factors for HFMD using epidemiological methods. We divided the country into three regions according to latitude and longitude because China is a vast country with wide-ranging environmental conditions. The results show that three regions (southern, central, and northern region) have a different seasonal distribution of HFMD epidemics. There were two peaks, one in May and the other in October, in the southern region of China which is similar geographically to Taiwan, Singapore and Viet Nam[10-14]. A single peak was observed in July in the northern region of China and this is similar to the situation in Mongolia. This indicates that seasonal distribution of HFMD is similar in regions which share similar latitude or climate conditions. In the southern region, the first peak was caused by infections of EV71, CoxA16, and other enteroviruses.

The second peak was mainly caused by EV71 infection, which was similar to observations in Vietnam[11]. These epidemiological features of HFMD could be extremely useful in alerting the relevant control agencies for predicting epidemics in the future.

The highest incidence rate and severity of HFMD cases in the central region were associated with a higher percentage of EV71 infections, higher population density, rural population, higher population under 6 years old and average temperature in 2008, compared with those in the southern and northern regions. We conclude that the epidemic situation of HFMD in a region was associated with multiple risk factors, such as population, climate and predominant pathogen.

Our results showed that 89.1% of HFMD cases occurred in children who are 0-4 years old with a male to female ratio of 1.7 to 2.0 in China. Severe cases occurred primarily (80.0%) in children <3 years of age. These results of risk age group of population and male to female ratio for HFMD were similar with previous studies carried out in Taiwan, Singapore, Viet Nam and other areas[10-11,15-17]. The incidence rate observed in the 0-4 age group (834.1/100 000) in mainland China was lower than the rate observed in Singapore (1460.5/100 000–5975.5/100 000, between 2001 and 2007)[12]. This could be related to the differences in the latitude and population density between mainland China and Singapore.

EV71 infection usually leads to autonomic nervous system deregulation, pulmonary hemorrhage and circulation failure. Our results showed that EV71 infection is a risk factor among both the severe and fatal case groups and this is consistent with other reports[10-13]. The average proportion of mortality among severe cases throughout China from May 2008 to April 2009 was 3.1%-12.5% and is less than the figures reported for Taiwan (31% in central Taiwan and 7.7% east of Taiwan) in 1998[14]. Rapid decrease in the proportion of deaths in severe cases, from 12.5% at the beginning of the outbreak to 2%-3% during the peak, might be attributable to the improved medical training and public education, as well as timely treatment during the latest epidemic in both towns and rural areas. This may also be responsible for the differences observed in the proportion of mortality in severe cases between mainland China and Taiwan.

Through comparison of clinical manifestations between severe and fatal cases, we highlighted some of the important signs for characterizing cases of HFMD as severe or fatal. These signs are helpful for identifying severe and critical cases of HFMD which need urgent medical support. For example, myoclonic jerks were a sign of CNS involvement, and a clear indication that patients with this symptom should be transferred to higher level hospitals for treatment. Tachypnea, lip purpling, pink foaming at mouth, and low limb temperature, were diagnostic of a critical case, which should be treated in pediatric intensive care unit (PICU).

One year's data are insufficient to fully understand the seasonal distribution of HFMD epidemics in China. Continuing surveillance of HFMD in the near future will be helpful for understanding the condition more clearly. The risk factors for HFMD epidemic were analyzed at a provincial level of climate and population, and could not explain the transmission patterns of HFMD at the community level. Community-based surveys of HFMD, will be an important part of future studies.

In conclusion, the large HFMD epidemic in China identified between May 2008 and April 2009 was caused primarily by EV71 infections and mainly occurred in young children in rural populations. Our analysis showed that children under 6 years of age in rural areas with EV71 infections are at the greatest risks of mortality. We suggest that specific medical intervention measures, including the development and distribution of effective vaccines, must be implemented to decrease the number of deaths from HFMD in this young rural population.

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