Glucocorticoid and Pyrazolone Treatment of Acute Fever is a Risk Factor for Critical and Life-Threatening Human Enterovirus 71 Infection During an Outbreak in China, 2008

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Background: Human enterovirus 71 (HEV71) causes outbreaks of life-threatening diseases throughout the world. The genesis of these severe diseases is unknown.

Methods: During an outbreak of HEV71 infection, we investigated risk factors for critical illness. We developed a modified pediatric index of mortality (mPIM) incorporating heart rate, temperature, white blood cell count, respiratory rate, chest infiltrates, skin color, reflexes, responsiveness, and mobility. We calculated the mPIM for 103 patients (22 deaths) using complete scoring criteria in the medical record. In a case–control study, we compared cases (mPIM $\geq$10 or death) with controls (mPIM = 0–9) by drugs received within 96 hours after onset of fever, initial temperature, age, and nutritional anthropometry.

Results: About 66% (68/103) of the patients with an mPIM score (28 cases and 40 controls) had data on initial exposures. About 50% of the 28 cases and 18% of the 40 controls received an injection to treat fever during the first 96 hours after onset (Odds ratio [OR] = 7.0, 95% confidence interval [CI]: 1.8–28). Injections containing exclusively glucocorticoids (OR = 4.8, 95% CI: 1.2–21) or pyrazolones (OR = 4.1, 95% CI: 0.91–19, P = 0.047) were risk factors for severe HEV71 infection. About 25% of cases and 5% of controls received both drugs parenterally while 7% of cases and 30% of controls received neither (OR = 21, 95% CI: 1.8–305). Conversely, cases and controls had identical average initial temperature, and did not differ significantly by age, sex, nutritional measurements, use of other drugs, or timeliness of medical care received.

Conclusion: Fever treatment with glucocorticoids and/or pyrazolones is a risk factor for life-threatening HEV71 infection.

Key Words: human enterovirus 71 infection, severity of disease, antipyretics, fever treatment, glucocorticoids, pyrazolones

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The epidemic of human enterovirus 71 (HEV71) infection has produced a puzzling epidemiologic pattern. In many regions of the world, the disease has manifested as mild hand, foot, and mouth disease (HFMD) or herpangina, with rare, sporadic cases of neurologic disease.[1–10] Other areas (eg, Taiwan, Sarawak, Bulgaria, and Hungary) have experienced outbreaks of severe, life-threatening disease that included bulbar paralysis, brainstem encephalitis and acute respiratory failure, and excess mortality.[11–16] Investigations of the severity of the disease have focused on differences in viral strains or genomes, and have been largely unsuccessful in explaining the genesis of severe neurologic disease and respiratory failure.[17–19] Outside of virologic investigations 2 reports of previous HEV71 investigations have explored coinfection and intensity of exposure but did not show clear associations with severe disease.[19,20]

In Spring 2008, a large outbreak of HFMD due to HEV71, with more than 7000 reported cases, including 23 deaths, occurred in Fuyang Prefecture in the Anhui Province, Southeast China. All deceased children had rapid onset of neurologic, respiratory, and circulatory system failure 3 to 10 days after onset of fever. Initial case investigations revealed that a notable proportion had received glucocorticoids and pyrazolones as outpatients before they developed indicators of severe disease. These drugs are commonly used by rural practitioners in China to treat fever.

MATERIALS AND METHODS

During this outbreak, HEV71 infections and severe HEV71 infections were diagnosed by healthcare providers treating the patients, based on the Guidelines for the Clinical Diagnosis and Treatment of HFMD/Herpangina by the Ministry of Health of China.[21] A probable HEV71 infection was development of the following signs and symptoms between March 1 and June 3, 2008 in a resident of Fuyang: Fever and vesicular rash on the hands, feet, mouth, or buttocks; or fever followed by brainstem encephalitis, acute pulmonary failure, or death. A confirmed HEV71 infection was a probable HEV71 infection with HEV71 nucleotides detected by real time reverse transcription polymerase chain reaction (RT-PCR), or HEV71 isolated by viral culture from stool, throat swab, or blood specimens at provincial or national laboratories. A severe HEV71 infection was a probable or confirmed HEV71 infection with $\geq$1 of the following findings: (1) prolonged high body temperature; (2) increasing muscle weakness, tremor, seizure; altered consciousness; weak or absent deep tendon reflexes, signs of meningeal irritation; (3) facial pallor, increased heart rate, impaired peripheral circulation, or abnormal blood pressure; (4) Difficult or irregular breathing, cyanosis, increased moist rales, or signs of pulmonary consolidation; (5) peripheral white blood cell count $>15 \times 10^9$/L or $<2 \times 10^9$/L); (6) Blood sugar >9 mmol/L; and (7) Rapidly worsening chest radiograph abnormality.

For our investigation, we included all 134 patients with severe HEV71 infections, who were admitted to 2 referral hospi-

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tals designated for treating severe HEV71 infections in Fuyang between March 1 and June 3, 2008. These included the 23 patients who died between March 27 and May 3.

We combined components of 2 validated scoring systems for severe pediatric disease[22,23] to create a modified pediatric index of mortality (mPIM) score to evaluate the relative severity of HEV71 infections (Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/A360). From each scoring system, we selected clinical indicators that were available on most of the severe HEV71 infected patients, excluding indicators that reflected chronic underlying disease. We grouped the indicators by organ system (pulmonary, cardiovascular, central nervous system) and inflammatory response. The total possible scores for each group were different. Accordingly, we equalized the contribution of each group by multiplying the observed score by the ratio 6/(maximum score). The final score was the sum of the equalized group scores. In the chart review, we selected the most extreme value for each criterion during the entire course of the hospitalization. If the patient died, we used the last value of the indicator before death. If a specific intervention precluded or altered assessment of an indicator, we used the last value before the intervention. The final scores were computed by a member of the study team (F.H.) using the data extracted from the patients' medical charts.

Using aforementioned, reported severe cases from the 2 hospitals, we conducted a case–control investigation to assess risk factors for critical HEV71 infection during this outbreak. The case-patients were those who died or whose mPIM scores were ≥10 points and termed critical cases. The control-patients were the survivors with an mPIM score <10 points. The main risk factors of interest were glucocorticoids (dexamethasone and methyl prednisolone) and pyrazolones (aminopyrine or dipyrone) used as parenteral antipyretics. We analyzed the use of these 2 groups of drugs when the patients consulted rural clinics or hospital outpatient departments within 0 to 96 hours after onset of the first symptom. We also assessed the use of other drugs, including antibiotics, antiviral drugs, and oral antipyretics, at initial visits to the clinics. Additionally, we compared case-patients with control-patients regarding their age, sex, *Z* score for weight for age, timeliness of initial clinic visit, and timeliness of hospital admission.

We used the Fisher exact test to evaluate all discrete variables, the exact Cochran-Armitage trend test to assess the statistical significance of trends, and the Kruskal-Wallis test to evaluate differences in mPIM score and other numerically ordered variables.

This investigation involved the response to a public health emergency and accordingly was exempt from the requirement for institutional review. The investigation was funded through general funds for emergency public health response of the Ministry of Health of China.

RESULTS

From March 1 to June 3, 2008, 7232 children in Fuyang Prefecture contracted HEV71 infections (6955 probable, 277 confirmed, and 134 severe), with 23 deaths (case fatality rate: 3.2/1000). About 69% (4997) were admitted to secondary and tertiary hospitals. All 179 townships in Fuyang Prefecture had probable or confirmed HEV71 infections; 28% of the townships reported severe HEV71 infections. Among children <6 years old the attack rate was 59/10,000 (4650 HFMD). Of the 23 deceased children, 22 (96%) were <3 years of age. RT-PCR detected HEV71 in 84% of the 209 mild, 53% of the 177 hospitalized, and 69% of the 13 deceased patients (including 4 without a rash) for whom specimens were available. Tests for Coxsackie A16 or other enteroviruses were negative.

HEV71 infections from March 1 to April 20 were identified retrospectively. During this period, reports of severe HEV71 infections, having been identified at hospitals, predominated. On April 21, all HFMD/herpangina cases became reportable, a rapid increase in the case count ensued. To control the outbreak and reduce mortality, on April 28, the government ordered the doctors at village and private clinics and township hospitals to stop treating febrile pediatric patients, and to refer these patients to the secondary and tertiary level hospitals, where medical care was of higher quality. During the week that followed, the total HEV71 infections continued to rise; however, the incidence of severe HEV71 infections dropped (Fig. 1). Based on this observation and on a review of initial treatment of fatal cases that showed glucocorticoid and pyrazolone treatment for initial fever, we developed a hypothesis that treatment of uncomplicated patients, initial fever was a risk factor for subsequent critical disease.

Of the 111 hospitalized surviving patients and 23 fatalities, 77% (103/134) had sufficient data to calculate an mPIM score. All deceased patients scored ≥10 points. Thus, we classified all patients (16 alive and 22 dead) whose mPIM score was ≥10 points

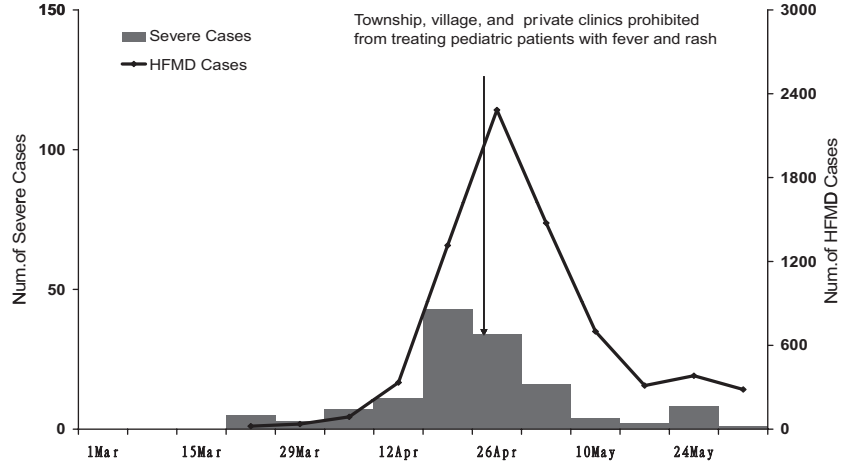

FIGURE 1. Epidemic curve of hand, foot, and mouth disease outbreak: Fuyang, China, 2008.

TABLE 1. Clinical Characteristics of 38 Cases (mPIM Score: ≥10) and 65 Controls (mPIM Score: 0–9) and Corresponding mPIM Score for Severe Human Enterovirus 71 Outbreak, March 1 to June 3, 2008, Fuyang, China

	Number		Percent		OR	95% CI	mPIM* Range	Median mPIM*
	Case (mPIM* ≥10) (n = 38)	Control (mPIM* <10) (n = 65)	Case (mPIM* ≥10)	Control (mPIM* <10)				
Fever	38	65	100	100	1.0	—	0–18	6.6
≥39°C	21	17	55	27	3.4	1.5–8.0	0–18	12
Rash	25	61	66	94	0.13	0.038–0.42	0–18	5.8
Meningitis	11	12	29	19	1.8	0.70–4.6	1.5–17	6.3
Encephalitis	6	13	16	20	0.75	0.26–2.2	2.0–17	6.0
Pulmonary edema†	19	11	50	17	4.9	2.0–12	2.6–17	12
Acute flaccid paralysis	13	6	34	9.2	5.1	1.7–15	3.1–17	12

*Modified pediatric index of mortality.
†Frothy blood tinged sputum with bilateral pulmonary infiltrates.
mPIM indicates modified pediatric index of mortality.

TABLE 2. Characteristics of Patients at First Treatment and at Subsequent Hospital Admission for 38 Cases (mPIM Score: ≥10) and 65 Controls (mPIM: 0–9), Human Enterovirus 71 Outbreak, March 1 to June 3, 2008, Fuyang, China

Characteristic	Statistic	Cases (mPIM ≥10) (n = 38)	Controls (mPIM <10) (n = 65)	*P*
Host factors				
Age (months)	Median	16	18	0.28
	Range	3–43	6–78	
Girls	% (n)	43 (16)	34 (22)	0.36
Weight-for-age *Z* score	Median	0	0	0.13
	Range	−2.6–0.99	−5.0–3.3	
No. family (persons)	Median	5	4	0.12
	Range	2–10	2–9	
First treatment				
Temperature (C) at first clinic visit	Median	38.0	38.0	0.41
	Range	37.3–39.5	36.6–39.4	
Days from onset to first clinic visit	Median	0	0	0.90
	Range	0–7	0–7	
First treatment received at				
Village clinics	% (n)	92 (35)	57 (37)	0.002
Primary hospitals	% (n)	5.3 (2)	20 (13)	0.48
Secondary or tertiary hospitals	% (n)	2.6 (1)	23 (15)	Ref
At hospital admission for severe disease				
Days from first clinic visit to hospitalization	Median	2.0	2.0	0.11
	Range	0–15	0–8	
Temperature (C)	Median	38.5	38.0	0.05
	Range	36.8–40.1	36.4–39.8	
Leucocyte count ($\times 10^9$)	Median	20.1	11.8	0.00
	Range	3.7–30.2	3.8–39.8	

mPIM indicates modified pediatric index of mortality.

as critical patients. Pulmonary edema and acute flaccid paralysis were more common among the critical patients, whereas rash was more common among the other 65 patients who scored <10 points (Table 1). The mPIM scores corresponded well with clinicians' treatment decisions: 58% (22/38) of the patients with an mPIM score ≥10, compared with 18% (12/65) of the other patients with an mPIM score <10, received mechanical ventilation.

In our case–control study of risk factors for severe HEV71 infection, 38 patients with mPIM scores ≥10 were classified as critical patients and the remaining 65 patients as control-patients. Of the 28 case-patients, 18 (64%) and 47 (90%) of the 52 control-patients for whom specimens were available were confirmed to have HEV71 infection by RT-PCR. Critical patients and control-patients had identical average initial body temperature that was recorded when they received their first treatment (Table 2). Other data reflecting severity were not recorded for these initial consultations.

We obtained information on drugs administered for 28 critical patients and 40 control-patients before the patients consulted for severe disease. Critical-patients were more likely than control-patients to have received parenteral antipyretic drugs (including glucocorticoids used for fever reduction) within 96 hours of initial symptom onset (odds ratio = 7.0, 95% confidence interval: 1.8–28) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A361). Also, the median mPIM score was 12.9 for parenteral compared with 3.3 for oral antipyretic treatment ($P < 0.001$). Only 2 drug types, glucocorticoids and pyrazolones, were used as parenteral antipyretics. Both drug types were significantly associated with subsequent development of higher mPIM scores and with being a critical patient. If both drugs were given to the same patient, the risk of critical illness was greatly increased (Odds ratio = 21) in comparison to using neither drug. We had insufficient data to estimate risk for each drug alone. About 90% of the critical

patients received their first consultations at village clinics (where doctors are more likely to prescribe glucocorticoids and pyrazolones) compared with 56% of control-patients.

We observed a trend of decreasing risk with the time after symptom onset that the first dose of glucocorticoid was received. All 7 critical-patients and zero control-patients received parenteral glucocorticoids during the first 48 hours after symptom onset compared with 3 critical patients and 4 control-patients from 48 to 71 hours and 1 critical patient and 8 control-patients from 72 to 96 hours ($P < 0.001$ by exact Cochran-Armitage trend test). In general, dexamethasone was more commonly given early in the course of the illness and methyl prednisolone later. We did not detect a similar time trend with pyrazolones. We were not able to retrieve the actual dose of glucocorticoids or pyrazolones given to these patients but it was common practice to administer up to 50 mg of dexamethasone and up to 550 mg of aminopyrine for fever reduction.

Use of all other types of drugs during early mild disease, did not differ significantly between critical patients and control-patients (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A361). They were also similar in the timing of their initial consultations and hospital admission, age, sex, and nutritional status.

DISCUSSION

During this HEV71 outbreak that featured unusually high proportions of severe disease and death, patients who received injections of glucocorticoids and pyrazolones to treat fever during the early, mild stages of disease development had increased risk of subsequent critical illness or death. The effect of both drugs given to the same patient was exceptionally strong, suggesting a synergistic effect. Since patients were similar with respect to symptoms, timeliness of consultation, and other factors, we doubt that confounding by indication or a competing cause could explain the observed association.

Innate immunity is the critical first defense against the multiplication and dissemination of infectious agents in the host. Deficiencies in innate immunity have been associated with more severe HEV71 infections in observational studies of humans and in an experimental mouse model.[24–26] Glucocorticoids impair innate immunity by inhibiting the activity of multiple cells of the innate immune system and suppressing the secretion of diverse immune mediators.[27] Accordingly, glucocorticoids should not be used to treat simple fevers, despite their potent antipyretic action.[28,29] Since dexamethasone is long acting (48 hours) and was often given in high dosage on the day of fever onset, this effect on innate immunity might have been strong.

Experimental results from a mouse model of HEV71 infection replicate the universal harmful effect of early administration of glucocorticoids on viral infections in mammals. Mice given dexamethasone 2 to 4 days after HEV71 exposure developed substantially higher viral loads in the muscle than control-mice; moreover, HEV71 was detected in the brain of dexamethasone-treated mice, whereas no HEV71 was found in the brain of the control-mice.[25] Since severe HEV71 infection in humans develops progressively from the spinal cord (24 hours postinfection) to the brainstem (72 hours postinfection),[30] early administration of glucocorticoids could also partially account for more rapid and extensive development of neurologic disease.

Use of glucocorticoids to treat acute fever in China is a widespread off-label (including Chinese labeling) practice, as shown in both the current and a previously published investigation.[31] Outside of China glucocorticoids are rarely used to treat acute fever. Receiving systemic glucocorticoid therapy for any condition increases the risk of severe infection.[32] We expect that this finding also applies to HEV71 infections.

Pyrazolone treatment of pediatric fever is also highly prevalent in China. Pyrazolones also affect the innate immune system.[33–35] However, other than rapidly developing agranulocytosis, for which reason these drugs have been banned in many countries,[36] the mechanism is less well understood than that of glucocorticoids. Although pyrazolone-induced agranulocytosis is relatively rare, the mechanism includes binding of pyrazolone derivatives to neutrophils, triggering a type II hypersensitivity reaction in which antibodies attack the target cells.[37,38] This immune reaction could interfere with neutrophil activity. A different mechanism might have been involved in the observed induction of dengue hemorrhagic fever by early administration of dipyrone to treat initial symptoms of dengue fever.[39] If they continue to be used as parenteral antipyretics, more observational and experimental work is needed to assess the risk of severe infection.

In addition to not being able to separate the effect of glucocorticoids and pyrazolones, our study has several limitations. First, some patients did not have an HEV71 isolate and did not have symptoms of HFMD or herpangina. Researchers have suggested that Japanese B encephalitis should be considered in Asian children with acute neurologic symptoms,[40] but Japanese B encephalitis occurs principally in summer months in Anhui Province,[41] as do neurotropic enteroviruses. Japanese B encephalitis vaccine is routinely offered to Fuyang children in the late winter. Recent receipt of Japanese B encephalitis vaccine was included in our initial hypothesis generating investigation, which did not suggest that it was either a protective or adverse factor.

Second, our data were retrospectively extracted from clinic records and through interviews using unstructured questionnaires. History of parenteral antipyretics use was not available for 21% of the case-patients and 13% of the control-patients. In a sensitivity analysis, use of parenteral antipyretics for initial treatment of fever remained statistically significant if we included all "unknowns" as "not taken." Since the only parenteral antipyretics used were glucocorticoids or pyrazolones, this limitation mainly affects the ability of the data to distinguish between the effects of the individual drugs.

Third, due to the retrospective nature of our investigation, data were unavailable to compute an mPIM score at the time of early drug administration, which would have been ideal.

Fourth, our control-patients were hospitalized patients with lower mPIM scores. Ideal control-patients would have been uncomplicated HEV71 infections or an unbiased sample from all HEV71 infections. Among the mild HEV71 infections, a finite but unknown proportion of patients never received any drug. The fact that all patients with severe HEV71 infections had received early treatment indicates that the bias would have reduced the observed odds ratios.

HEV71 involves wide-ranging clinical syndromes. The term "severe" might refer to high or prolonged fever or aseptic meningitis in 1 patient or brainstem encephalitis in another.[1,14,16] Surveillance definitions often use the presence of one or more of the different clinical entities, a pattern that the Chinese Ministry of Health has followed.[16,42] Each clinical entity is also prone to major variation in severity. Accordingly, we constructed a scoring system to reduce subjectivity in assessing severity. This scoring system used physiologic variables from clinical scores that were designed for other purposes than to quantify maximum severity. The score worked well in identifying drugs both in using a cut-off value and in comparing median scores. However, this severity score was not validated. Future studies of severe HEV 71 will need

to strengthen the reliability of findings with the use of validated clinical severity scores.

Fever is a natural defense mechanism of the body against the invasion of pathogens. Experimental and clinical data suggest that fever can help humans[43] and warm-blooded vertebrates[44] recovery faster from infections. Fever appears to improve the effectiveness of certain immune response mechanisms, and enhance the immune response targeting the infected site during the acute phase,[45] thereby speeding up the inflammatory defenses.[46] A recent Finnish study suggested that fever is a protective factor from death in bacterial infections.[47] Researchers agree that both aggressive treatment of fever and too little fever control are detrimental.[43,48] Current recommendations for otherwise healthy children advise no antipyretic treatment for temperatures <39°C, discretionary use of antipyretics to relieve the discomfort for temperatures from 39°C to 41°C, and universal antipyretic treatment for temperatures >41°C. The recommended antipyretics for children are acetaminophen (paracetamol) and ibuprofen.[49]

In summary, early use of glucocorticoids or glucocorticoids plus pyrazolones by rural practitioners in China was associated with increased risk of subsequent severe disease or death. The findings of this study, combined with experimental data and the clinical experience in the United States and other countries, strongly suggest that corticosteroids and pyrazolones should not be used to treat fever in children. We recommend that guidelines for pediatric fever treatment similar to the ones in Western countries[49] should be adopted and enforced in China, especially in village clinics.

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