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REVIEW ARTICLE

Chinese guidelines for the diagnosis and treatment of hand, foot and mouth disease (2018 edition)

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Abstract

Background Hand, foot, and mouth disease (HFMD) is a common infectious disease in childhood caused by an enterovirus (EV), and which is principally seen in children under 5 years of age. To promote diagnostic awareness and effective treatments, to further standardize and strengthen the clinical management and to reduce the mortality of HFMD, the guidelines for diagnosis and treatment have been developed.

Methods National Health Commission of China assembled an expert committee for a revision of the guidelines. The committee included 33 members who are specialized in diagnosis and treatment of HFMD.

Results Early recognition of severe cases is utmost important in diagnosis and treatment of patients with HFMD. The key to diagnosis and treatment of severe cases lies in the timely and accurate recognition of stages 2 and 3 of HFMD, in order to stop progression to stage 4. Clinicians should particularly pay attention to those EV-A71 cases in children aged less than 3 years, and those with disease duration less than 3 days. The following indicators should alert the clinician of possible deterioration and impending critical disease: (1) persistent hyperthermia; (2) involvement of nervous system; (3) worsening respiratory rate and rhythm; (4) circulatory dysfunction; (5) elevated peripheral WBC count; (6) elevated blood glucose and (7) elevated blood lactic acid. For treatment, most mild cases can be treated as outpatients. Patients should be isolated to avoid cross-infection. Intense treatment modalities should be given for those severe cases.

Conclusion The guidelines can provide systematic guidance on the diagnosis and management of HFMD.

Keywords Diagnosis · Guidelines · HFMD · Treatment

Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious disease in childhood caused by an enterovirus (EV), and which is principally seen in children under 5 years of age; HFMD is encountered across the globe. It is prevalent in all parts of China, where the disease is perennial with an incidence rate varying between 37/100,000 and 205/100,000 while mortality in recent years has ranged between 6.5/100,000 and 51/100,000. With a view to promoting diagnostic awareness and effective treatments, and to further standardize and improve HFMD clinical management and reduce mortality, new guidelines have been developed. The current guidelines are based upon and incorporate the most recent advances in HFMD diagnosis and management.

Etiology

HFMD is caused by an enterovirus infection. Enteroviruses belong to enterovirus genus of the picornavirus ("small RNA virus") family. The main serotypes responsible for the disease include enteroviruses in the coxsackievirus (CV) group A, type 4–7, 9, 10, and 16 as well as group B types 1–3, and 5, some echovirus serotypes, and enterovirus A71 (EV-A71). The most commonly encountered are CV-A16 and EV-A71, with the latter accounting for the majority of severe

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and fatal cases of HFMD. CV-A6 and CV-A10 case burden has increased significantly in some areas in recent years. There is no protective cross immunity between the different enteroviruses types [1–6].

Epidemiology

Infection sources

Children are the main source of infection. Infection may be overt, subclinical or latent. The latent infection rate of HFMD is high. Enterovirus can survive in hydrothermal conditions. The virus is transmitted via the feces, throat secretions, saliva and potentially other bodily fluids of infected individuals [7].

Route of transmission

Close contact is usually required for transmission. The infection can be contracted by contact with virus-contaminated hands, towels, handkerchiefs, dental cleaning paraphernalia, toys, tableware, bedding and underwear amongst others. It can also be transmitted via contaminated respiratory droplets, water, and food [8].

Susceptible population

Infants and children are generally considered the most susceptible, especially the children less than 5 years of age [9].

Pathogenesis and pathological changes

Pathogenesis

At the initiation of infection, an enterovirus binds to virus receptor on the surface of pharyngeal and intestinal epithelial cells. The main virus receptors of EV-A71 and CV-A16 include human scavenger receptor class B2 (SCARB2) and P-selectin glycoprotein ligand-1 (PSGL-1). The virus is absorbed into the cell via endocytosis after receptor binding. The viral genome is released, replicated, transcribed and translated to produce viral proteins. The newly formed viral genome and proteins are assembled into virus particles in the cytoplasm [10, 11]. Enterovirus replicates mainly in the lymph nodes of the tonsils, pharynx and intestine. It is then released into the bloodstream and spread to skin, mucous membranes, the nervous system, the respiratory tract, heart, liver, pancreas, adrenal gland among other sites, etc. An inflammatory response in infected organs may cause clinical symptoms and organ-related complications. In rare cases, it may lead to organ system failure, e.g., cardiopulmonary failure occasioned by vasomotor dysfunction following nervous system injury [12, 13], or massive release of inflammatory mediators such as containing interleukin (IL)-10, IL-13 and interferon (IFN)-γ. Neurogenic pulmonary edema and circulatory failure are the main causes of death in children with HFMD. The precise pathophysiological mechanisms at play in such cases are complex and multifactorial [14, 15].

Pathological changes

Autopsy with histopathological examination may display evidence of lymphocyte degeneration and necrosis, especially in gastrointestinal and mesenteric lymph nodes. The main pathological features observed in nervous tissue include various degree of inflammatory response with a neurotropic pattern showing evidence of neuronal apoptosis, nodular hyperplasia of monocytes and microglia, vascular cuffing, cerebral edema and cerebellar tonsil hernia. The main observation in lung includes pulmonary edema, congestion, and hemorrhage with inflammatory cellular infiltration. Myocardial rupture and edema, necrotizing enteritis, and the severe degeneration and necrosis of kidney, adrenal, spleen and liver can also occur [16–21].

Clinical manifestations

Incubation period

Incubation period is typically 2–10 days, with an average of 3–5 days [22].

Clinical symptoms and signs

Clinical staging is as below:

Stage 1: Eruption

The main symptoms include fever and eruption on the hands, feet, mouth, and buttocks. The oral rash is an enanthem and may be isolated, constituting herpangina. Symptoms may include cough, rhinorrhea, anorexia, and non-specific systemic symptoms. In some cases, the infection may manifest only with a rash or as herpangina. A rash is not inevitable and is not seen in all cases.

The typical rash is maculo-papular and may be vesicular. An inflammatory cuff may surround the vesicles, which may contain little fluid. The rash may be non-pruritic and painless. Resolution, which occurs without scab formation, does not lead to scarring. Atypical rash appearance may occur, being generally less severe, with smaller lesions that are somewhat indurated. Occasionally petechiae and ecchymoses may be evident. Some types of enterovirus, such as

CV-A6 and CV-A10, may cause severe skin lesions, with bullous change accompanied by pain and pruritis with extension beyond the hand, foot, and mouth [23].

This stage represents the commonest clinical picture seen in HMFD. Most such cases resolve of their own accord at this stage.

Stage 2: Nervous system involvement

Central nervous system (CNS) injury and complications may occur. This is typically seen 1–5 days after infection; symptoms include lethargy, sucking weakness, ease of being startled, headache, vomiting, irritability, limb tremors, myopathy, and nuchal rigidity, etc. Some cases may display signs of more extensive or severe neurological injury. The above clinical picture represents the classic image of severe HFMD, although most cases will resolve.

Stage 3: Early cardiopulmonary failure

This usually occurs within the first 5 days of the illness with increased heart and respiratory rates, cold sweats, cold extremities, mottled skin, and increased blood pressure. This stage represents the critical stage of HFMD. The key to reduce mortality is recognition with early diagnosis and appropriate management.

Stage 4: Cardiopulmonary failure

HFMD may progress rapidly from stage 3 to 4. Symptoms include tachycardia (bradycardia is also occasionally seen), tachypnea, cyanosis, cough with pink foamy or even bloody sputum, hypotension and ultimately cardiovascular collapse. Some cases may exhibit severe encephalopathy; convulsions and coma may supervene. This stage constitutes critical HFMD and is accompanied by high mortality.

Stage 5: Recovery

Fever gradually subsides and dependence on cardiovascular support recedes. CNS and cardiopulmonary function gradually recover, although neurological sequelae may remain in some cases. Piptonychia may follow some cases of HFMD (especially those due to CV-A6 and CV-A10), typically 2–4 weeks after infection, with new nails emerging 1–2 months thereafter.

Most infected children enjoy a favorable prognosis and recovery without sequelae, generally within 1 week. With rapid progression and severe disease, a small minority of children may suffer CNS injury; such children may present with signs and symptoms of brainstem encephalitis, encephalomyelitis, cerebrospinal meningitis, or other severe neurological disorder. Mortality rate is high in such children, typically from circulatory failure or neurogenic pulmonary edema [24].

Diagnostic tests [25]

Laboratory test

Routine blood tests and C-reactive protein (CRP)

The white blood cell count is normal in most cases. In some cases, a leukocytosis with neutrophilia may be observed. CRP elevation may be seen.

Blood biochemical examination

Mild elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase isoenzyme MB (CK-MB) may occur in some cases. In severe cases, elevations in troponin, blood glucose and lactic acid are seen.

Cerebrospinal fluid (CSF) analysis

Cerebrospinal fluid changes will accompany CNS involvement and injury. CSF pressure is typically increased with an elevated WBC count (mainly monocytic but multinucleate in early stages). Normal or slightly increased protein, normal glucose and chloride are seen which is consistent with viral meningitis and/or encephalitis.

Blood gas analysis

Arterial oxygen partial pressure decreases when the respiratory system is involved and in severe cases, decreased blood oxygen saturation and increased partial carbon dioxide pressure with acidosis are seen.

Virologic and serologic examination

Specific enterovirus nucleic acid detection may be conducted on clinical specimens: throat swab, stool, anal swab, and blood. Enterovirus may also be isolated and cultured. IgM-specific antibody should be positive during the acute phase; during the recovery phase neutralizing antibody directed against CV-A16, EV-A71 and other HFMD-relevant enteroviruses should exhibit at least a fourfold magnitude increase in titre compared with the titer obtained during the acute stage.

Imaging

Chest imaging

No obvious abnormality in lungs of children is likely to be seen in mild cases. Severe and critical cases complicated by neurogenic pulmonary edema are likely to show decreased radiolucency with ground-glass opacities in both lung fields; patchy change may show limited or extensive distribution. Pulmonary lesions may progress rapidly.

Cerebral CT and/or MRI

Cerebral CT imaging may be used to identify intracranial hemorrhage, cerebral hernia, and intracranial lesions. Abnormal MRI changes may be seen in patients with CNS involvement. Patients with brainstem encephalitis can be identified by spotty or patchy T1 and T2 signals in the pons, medulla oblongata and midbrain. Patients with acute flaccid paresis show spotty symmetric or asymmetric T1 and T2 signals in the anterior horn of the involved segments of the spinal cord.

Electrocardiography (ECG)

Generally, this will show sinus tachycardia or bradycardia, Q–T interval prolongation, and ST–T segment change.

Electroencephalography (EEG)

Those patients with nervous system involvement generally show diffuse slow waves, while some may show spikes, or sharp slow waves.

Echocardiography

Severely ill patients may demonstrate myocardial systolic and/or diastolic dysfunction, regional wall motion abnormalities, and decreased ejection fraction amongst other abnormalities.

Diagnostic criteria

Diagnosis can be made based on current epidemiology, clinical manifestation and virological investigation.

Clinically diagnosed cases

Epidemiological history

These are common in preschoolers, especially in infants. During epidemics, increased incidence may be detected in local nurseries and the children's contacts. A history of either direct or indirect contact with infected persons prior to illness onset may be ascertained.

Clinical manifestations

This will largely conform to the clinical descriptions provided above, in the clinical staging section. In rare cases, the rash will have an atypical appearance, while some cases will present with either encephalitis or meningitis. In these atypical cases, the diagnosis will need to be confirmed by virological or serological means.

Confirmed cases

On the basis of clinical diagnosis, the infection can be confirmed if it meets one of the following criteria: (1) detection of specific enterovirus nucleic acid sequences (CV-A16, EV-A71, etc). (2) Isolation and identification of enterovirus such as CV-A16, EV-A71 or other type that could cause HFMD; (3) presence of IgM antibody against disease-related virus during the acute stage; (4) presence of neutralizing antibody titer against the relevant enterovirus in the recovery phase is at least four times higher than that in the acute stage.

Differential diagnosis

Other childhood exanthemata

HFMD should be differentiated from other exanthemata seen in childhood. This may include papular urticaria, sand rash, chicken pox, atypical measles, exanthema subitum, herpes zoster, rubella and Kawasaki disease. Bullous rashes caused by CV-A6 or CV-A10 should be differentiated from chickenpox. HFMD should be differentiated from herpes simplex when perioral lesions are present. The differential diagnosis is guided by investigation, including virology and serology [26].

Encephalitis or meningitis caused by other viruses

The clinical manifestation of encephalitis or meningitis caused by viruses such as herpes simplex virus, cytomegalovirus (CMV) and Epstein–Barr virus (EBV) is likely to be similar to those seen in severe cases of HFMD with CNS involvement. For patients with atypical rash, diagnosis can be assisted by the history and early virological investigation for the presence of enterovirus, especially EV-A71. Diagnosis should be made based on the results of virological or serological investigations.

Poliomyelitis

When the severe case of HFMD is complicated with acute flaccid paralysis, it needs to be differentiated from poliomyelitis.

The latter mainly manifested as bimodal fever and flaccid paralysis occurs in the process of defervescence at the second week or before. The condition gets the worst after fever and there is no rash [27].

Pneumonia

The neurogenic pulmonary edema which may accompany severe HFMD should be differentiated from pneumonia. Children with pneumonia generally do not exhibit a rash. Chest radiography examination may show consolidation, atelectasis, and pleural effusion, with gradual evolution of the image [28].

Early recognition of severe cases [29–32]

The key to diagnosis and treatment of severe cases lies in the timely and accurate recognition of stages 2 and 3 of HFMD, in order to combat progression to stage 4. Clinicians should be especially concerned by EV-A71 cases in children aged less than 3 years, and cases of less than 3 days duration.

The following indicators should alert the clinician of possible deterioration and impending critical disease: (1) persistent hyperthermia: fever greater than 39 °C with poor response to antipyretics; (2) involvement of nervous system: symptoms may include headache, nystagmus or upward gaze diversion, vomiting, lethargy, ease of being startled, limb tremor, sucking weakness, and instability of posture, e.g., standing or sitting, amongst others; (3) abnormal respiratory rate and rhythm: rapid, slow, or irregular breath. The respiratory rate may exceed 30–40/min in the resting state; (4) circulatory dysfunction: increased heart rate (> 160 times/minute), cold sweats, cold extremities, mottled skin, elevated blood pressure, prolonged capillary filling time (> 2 seconds); (5) elevated peripheral WBC count: peripheral WBC count may exceed 15×10^9/L in the absence of any other infectious etiology; (6) elevated blood glucose: stress hyperglycemia may be evident, with blood glucose > 8.3 mmol/L; (7) elevated blood lactic acid: blood lactic acid is generally ≥ 2.0 mmol/L when circulatory dysfunction exists. Increased levels are of worse prognostic significance.

Treatment

General treatment

Most HFMD cases can be treated as outpatients. Patients should be isolated to avoid cross-infection. Attention to nutrition as well as oral and skin care is recommended.

Fever should be actively managed. Physical cooling, e.g., warm water sponge baths, fever cooling patches, fanning and antipyretics are appropriate for children whose temperature exceeds 38.5 °C. Commonly used drugs include: ibuprofen 5–10 mg/kg, acetaminophen 10–15 mg/kg. The minimum interval between two doses is 6 hours.

Keep the children in a quiet and restful state. Seizures should be controlled immediately. Commonly used drugs are as follows: if no venous access is available, the first choice is intramuscular midazolam, 0.1–0.3 mg/kg. The maximum single dose is 5 mg in patients > 40 kg while administration of 10 mg is recommended for those with body weight > 40 kg. Another option is the slow intravenous injection of diazepam at 0.3–0.5 mg/kg with the maximum single dose being 10 mg; the injection rate should be 1–2 mg/minute. One should monitor vital signs closely and prepare for respiratory support. Chloral hydrate may also be used, and maintain a patent airway and administer oxygen if necessary. Pay attention to nutritional support to maintain fluid and electrolyte balance.

Antiviral treatment [33–43]

There is no specific anti-enterovirus drug available. Studies have shown that interferon alpha spray or atomization treatment, and ribavirin administrated intravenously may have some effect in the management of HFMD in the early stage. Close attention should be paid to ribavirin's adverse reactions including reproductive toxicity. Acyclovir, ganciclovir, and monosodium phosphate vidarabine have no place in the management of HFMD.

Fluid therapy

Cerebral edema, pulmonary edema and heart failure may appear in severe cases of HFMD, and fluid intake should be rigorously controlled. Physiological fluid requirement is 60–80 mL/kg/day in the absence of deliberate diuresis. Fluid should be infused at a constant rate of 2.5–3.3 mL/kg/hour, in the meantime to maintain perfusion. In cases with circulatory shock, resuscitate with normal saline 5–10 mL/kg/time over 15–30 minutes while using vasoactive agents; following initial administration, fluid therapy should be carefully managed to avoid overload. Colloidal fluid should be used if circulatory shock is not adequately controlled; examples include albumin or plasma.

Healthcare institutions may monitor indicators such as central venous pressure (CVP) and invasive arterial blood pressure (ABP) to guide fluid therapy.

Decreased intracranial pressure

20% mannitol is commonly used in 0.25–1.0 g/kg, q4h–q8h, as a rapid intravenous injection over 20–30 minutes to reduce increased intracranial pressure. The frequency may

be increased to q2h–q4h in the case of severe intracranial hypertension or cerebral herniation.

Treatment in combination with hypertonic saline (3% sodium chloride) may be considered for patients with severe intracranial hypertension or hyponatremia. Diuretics may be used in patients with cardiac overload, e.g., intravenous furosemide at 1–2 mg/kg.

Vasoactive agents

The hemodynamic change typically observed in stage 3 is that of high dynamic and high resistance, and mostly vasodilators should be considered in this period. Milrinone can be used with a loading dosage of 50–75 μg/kg, and the infusion should be completed within 15 minutes [44]. The maintenance dose starts from 0.25 μg/kg/min, and may be gradually adjusted up to 1 μg/kg/min. The total duration of infusion period should in general not exceed 72 hours. Blood pressure should be controlled to a level below that of constituting severe hypertension at the corresponding age (specific blood pressure values are shown in Table 1). Phentolamine (1–20 μg/kg/min) or sodium nitroprusside (0.5–5 μg/kg/min) can be initiated at a low dose and gradually increased to an appropriate dose level. Vital signs including blood pressure should be closely monitored during this period.

Hypotension may manifest in stage 4, in which case positive inotropic agents and vasopressors, such as dopamine at 5–20 μg/kg/min, norepinephrine at 0.05–2 μg/kg/min, adrenaline at 0.05–2 μg/kg/minute and dobutamine at 2.5–20 μg/kg/min may be used. The drug should be initiated at a low dose and gradually increased to the dose which supports adequate pressure and perfusion.

If the above drugs prove ineffective, vasopressin or levosimendan can be considered. Vasopressin, at 20 μg/kg, q4h, can be slowly administered intravenously; the duration of drug use depends on the hemodynamic improvement. Levosimendan's loading dose is at 6–12 μg/kg intravenously and the maintenance dose is 0.1 μg/kg/min.

Table 1 Definition of severe hypertension in children under 5 years

Gender	Age (y)	Blood pressure	
		Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Female	0–3	≥110	≥72
	>3	≥112	≥73
	>4	≥114	≥76
Male	0–3	≥112	≥73
	>4	≥114	≥74
	>5	≥117	≥77

Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulin is not recommended for routine use in stage 2 disease. Patients with encephalomyelitis and persistent high fever, and critical cases, may be considered for IVIG treatment. Dosage is at 1.0 g/kg/day for 2 days [45].

Corticosteroids

Patients with encephalomyelitis and persistent high fever, as well as critical cases, may be considered for treatment with corticosteroids: methylprednisolone at 1–2 mg/kg/day, or hydrocortisone at 3–5 mg/kg/day, or dexamethasone 0.2–0.5 mg/kg/day may be used for 3–5 days [46].

Mechanical ventilation

1. Indications: when the following clinical manifestations occur, tracheal intubation and mechanical ventilation may be initiated: (1) shortness of breath, deceleration or rhythm changes; (2) reddish or bloody airway secretion; (3) rapid development of moist rales; (4) obvious pulmonary exudative lesions on chest X-ray examination; (5) decrease in SpO_2 or PaO_2; (6) pallor, cyanosis, low skin temperature, mottled skin, decreased blood pressure; (7) frequent seizures or coma.
2. Mechanical ventilation mode: pressure control ventilation is commonly selected but other modes may also be selected. High frequency ventilation (HFV) could be considered in patients with inadequate aeration or refractory hypoxemia.
3. Target of mechanical ventilation parameter adjustment: maintain PaO_2 above 60–80 mmHg, SaO_2 above 92–97%. Control pulmonary edema and pulmonary hemorrhage.

   For patients with pulmonary edema or pulmonary hemorrhage or central respiratory failure, parameters should be adjusted according to the initial parameters table for mechanical ventilation (Table 2). If pulmonary hemorrhage is not controlled or blood oxygenation is not improved, PEEP can be increased to 1–2 cmH_2O each time, but generally not to exceed 20 cmH_2O. PIP should be adjusted at the same time to ensure normal oxygenation. Ventilator parameters should be gradually reduced once pulmonary edema and hemorrhage have been controlled.
4. Mechanical ventilation management: (1) analgesia and sedation: sufficient sedation and analgesia should be administered before tracheal intubation. Drugs include midazolam (intravenous injection at 0.1–0.3 mg/kg/hour), fentanyl (intravenous injection at 1–2 μg/kg, injection time > 60 seconds, with intravenous maintenance pump injection l–4 μg/kg/hour); (2) to avoid frequent and prolonged suction during mechanical ven-

Table 2 Initial parameters of ventilator in mechanical ventilation

Categories	Fraction of inspired oxygen (FiO_2) (%)	Peak inspiratory pressure (PIP)	Positive end-expiratory pressure (PEEP)	Respiratory frequency (f)	Tidal volume (Vt)
Pulmonary edema or pulmonary hemorrhage	60–100	20–30 cmH_2O (including PEEP)	8–2 cmH_2O	20–40 times/min	6–8 mL/kg
Central respiratory failure only	21–40	0–15 cmH_2O (including PEEP)	4–5 cmH_2O	20–40 times/min	6–8 mL/kg

tilation, which will reduce the airway pressure. Keep the airway open and prevent the endotracheal tube from being obstructed by blood clot.

5. Withdrawal indications: (1) spontaneous breathing returns to normal with a good cough reflex; (2) when oxygenation index (PaO_2/FiO_2) ≥ 200 mmHg and PEEP < 10 cmH_2O, weaning assessment should be started; (3) improved blood gas analysis and improvement of pulmonary effusion and edema on chest X-ray; (4) improved level of consciousness; (5) stable circulation.

Others

(1) Hemodialysis: continuous hemodialysis may be considered in critical cases, but there are no specific recommendations. Hemodialysis as an adjunctive treatment may help to reduce catecholamine storm and inflammation, assist fluid balance and replace kidney function. It is suitable for patients at stage 3 and 4 of HFMD; (2) extracorporeal life support: including extracorporeal membrane oxygenation (ECMO), extracorporeal left ventricular support (ECLVS), or ECMO + left ventricular decompression (LV vent). Extracorporeal life support is suitable for patients with severe heart failure who have failed routine treatment. ECMO + LV vent is suitable for critical cases with severe pulmonary edema and left heart failure. It is not recommended for children with severe encephalopathy.

Treatment during recovery phase

Rehabilitation and nursing care for patients in the recovery phase can promote the early recovery of organ function, especially of the nervous system.

Traditional Chinese medicine treatment

Based on the theory of traditional Chinese medicine (TCM), HFMD belongs to the category of "plague warm and clip wet". The characteristics of HFMD transmutation have the law of "defensive energy nutrients and blood", so it should be treated according to the disease progression stages.

1. Eruption stage: to damp the heat syndrome of spleen and lung.

   (1) Symptoms: papules and vesicles appear on hand and foot, in mouth, on buttocks and on other parts, with or without fever, burn-out, salivation, sore throat, anorexia, constipation. For some severe cases, big blisters and piptonychia can be seen; (2) tongue picture, pulse condition and fingerprint: the tongue has a pink or red color, greasy fur, rapid pulse, red or purple fingerprint; (3) treatment: heat-clearing, detoxification, and clearing dampness and evil; (4) basic prescription: Ganlu Xiaodu Micropill; (5) common drugs: Radix Scutellariae, Herba Artemisiae, Capillariae, Herba Pogostemonis, Fructus Forsythiae, Flos Lonicerae, Talcum, Fructus Arctii, Rhizoma Imperatae, Peppermint and Rhizoma Belamcanda; (6) usage: one prescription per day, decoct with 100–150 mL water, 3–4 times orally. Enema prescription also could be taken with decoction of 50–100 mL at 1 enema/day; (7) change of prescription: if there is a continuous high fever, irritability, halitosis, thirsty, constipation, it is possible to add Gypsum Fibrosum, golden thread, herbataching on the above prescriptions; (8) processed TCM drugs: additional processed TCM drugs that have been clinically studied and reported, can be used for the effect of heat-clearing, detoxicating and dissipating dampness and rash.
2. Wind syndrome stage: heat shock in the liver.

   (1) Symptoms: high fever, skittishness, muscle movement, infantile convulsions, or limb flaccidity, weakness, vomiting, somnolence, even confusion and coma; (2) tongue picture, pulse condition and fingerprint: dark red or deep red tongue, yellow or yellow greasy dry, stringy thin rapid pulse, fingerprint purple and stagnant; (3) treatment: cool blood for calming endogenous wind, clear away heat, dampness and toxic material; (4) basic prescription: antipyretic and antitoxic decoction with Cornus Antelopis and Uncariae Decoction; (5) commonly used drugs: antelope horn powder, gambir plant, gypsum, rhubarb root and rhizome, golden thread, tall

gastrodia tuber, scorpion, stiff silkworm, Cortex Moutan Radicis, Redroot gromwell root and dried rehmannia root; (6) added or reduced TCM medicine: if a patient has a continuous high fever with loss of consciousness, it is necessary to add Angong Niuhuang Wan on the above prescriptions. If with constipation, add Zixue Powder; (7) usage: one prescription/day, decoct with 100–150 ml water, 3–4 times orally. Enema prescription also could be used, decoction with 50–100 ml at one enema/day; (8) processed TCM drugs: it is recommended to treat with processed Chinese herbal medicine with the effect of heat-clearing, detoxicating and extinguishing wind to arrest convulsion if it has been clinically studied and reported.

3. Dyspnea collapse stage: evil influence into the heart and lung syndrome, deficiency of vital energy and yang exhausted.

   (1) Symptoms: high fever, dyspnea and tachypnea, coma, acrohypothermy, profuse perspiration, pale face, cyanosis of lips; (2) tongue picture, pulse condition and fingerprint: dyspnea, dark purple tongue, rapid pulse or sink and delayed pulse, dark purple fingerprint; (3) treatment: fixation, inducing resuscitation, and clear heat and detoxicate; (4) basic prescription: ginseng and Aconiti decoction, Sheng Mai powder and An Gong Niu Huang Wan; (5) common TCM drugs: ginseng, prepared common monkshood branched root, liriope root tuber, pulp of cornus, artificial bezoar, antelope horn powder, rhizoma coptis, curcuma aromatica, acorus gramineus soland, and curcuma aromatic; (6) usage: one prescription/day, decoct with 100–150 mL water, 3–4 times orally. Enema prescription also could be used with decoction of 50–100 mL at one enema/day; (7) processed TCM drugs: it is recommended that Chinese herbal medicine with effect of heat-clearing, nourishing Qi and warming Yang to solid off which must be clinically studied and reported.

4. Convalescence stage: Qi and Yin deficiency, collaterals obstruction.

   (1) Symptoms: fatigue, anorexia, or with limb flaccidity, or with limb numbness; (2) tongue picture, pulse condition and fingerprint: pale tongue, thin and greasy fur, thready pulse, and light or purple fingerprints; (3) treatment: tonifying Qi, nourishing Yin, and invigorating the spleen; (4) basic prescription: Sheng Mai powder and Qiwei Baizhu powder; (5) common drugs: Codonopsis pilosula, Schisandra chinensis, liriope root tuber, rhizoma atractylodes, poriacocos, polygonatum odoratum, Agastache rugosus, costus root and the root of kudzu vine; (6) usage: one prescription a day orally; decoct with 100–150 mL water, 3–4 times orally; (7) processed TCM drugs: Chinese herbal medicines with tonifying Qi, nourishing Yin and freeing channels can be used for treatment if their efficacy have been clinically studied and reported; (8) non-drug treatment: point massage and others help functional recovery.

The prescription drugs should be used according to patients' age, and only for treatment of HFMD, not for prevention.

Prevention

General precautions

Good personal hygiene habit is the key to prevent HFMD. Wash hands frequently, and prevent children from drinking unpurified water, and eating raw and cold food. Toys and other frequently contacted items should be cleaned and disinfected regularly. Keep children from contact with HFMD patients.

Vaccination

EV-A71 inactivated vaccine is available for children from 6 months to 5 years of age, to prevent HFMD caused by EV-A71. The basic immunization regimen is to administer two doses 1 month apart. Children are encouraged to complete vaccination before 12 months of age [47–52].

Hospital infection control

Healthcare institutions should be pro-active in the prevention and control of infection. Healthcare settings at all levels should rigorously identify and isolation of infected patients. There should be a special consulting room for suspected cases of HFMD. Whenever a hospital receives an HFMD case, standard preventive measure should be taken, by strictly following good hand hygiene and disinfection of the facility and related items. Effective disinfectants containing chlorine (bromine) should be selected. General disinfection with 75% ethanol or 5% lysol is ineffective against enterovirus.

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