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HAND, FOOT AND MOUTH DISEASE - A REVIEW

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ABSTRACT

Hand, foot and mouth disease (HFMD) is a contagious viral disease and mainly affects infants and young children. The main manifestations are fever, vesicular rashes on the hand, feet, and buttocks, and ulcers in the oral mucosa. Usually, HFMD is self-limiting, but a small proportion of children may experience severe complications such as meningitis, encephalitis, acute flaccid paralysis, and neurorespiratory syndrome. Historically, outbreaks of HFMD were mainly caused by two enteroviruses: the coxsackievirus A16 (CV-A16) and the enterovirus 71 (EVA71). In recent years, coxsackievirus A6 and coxsackievirus A10 have been widely associated with both sporadic cases and outbreaks of HFMD worldwide, particularly in India, South East Asia, and Europe with an increased frequency of neurological complications as well as mortality. Currently, there is no pharmacological intervention or vaccine available for HFMD. A formalin-inactivated EV-A71 vaccine has completed clinical trials in several Asian countries. However, this vaccine cannot protect major emerging etiologies of HFMD such as CV-A16, CV-A6, and CV-A10. Therefore, the development of a globally representative multivalent HFMD vaccine could be the best strategy. For a long time, hand, foot and mouth disease was seen as a mild viral infection.

KEYWORDS: Picoranaviridae family, Enterovirus genus, Real time PCR, NSAIDS (Non steroidal anti- inflammatory drugs), Pleconaril.

INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common contagious disease, affecting mainly children under the age of 10 and adults too, sometimes. The main manifestations are fever, vesicular rashes on hands, feet, and buttocks, and ulcers in the oral mucosa. Usually, HFMD is self-limiting, but a small proportion of children may experience severe complications such as meningitis, encephalitis, acute flaccid paralysis (AFP), and neurorespiratory syndrome.

Therefore, HFMD poses a serious threat to publichealth mainly in the WPRO region. HFMD is caused by enteroviruses (27–30 nm in size) consisting of single-stranded, positive-sense RNA. These viruses size) consisting of single-stranded, positive-sense RNA. These viruses belong to the Picornaviridae family.[1]

Traditionally, human enteroviruses were classified into many groups, based on pathogenicity in humans and laboratory animals and cytopathic effects. Subgroups are polioviruses (3 serotypes), coxsackievirus A viruses (23 serotypes), coxsackievirus B viruses (6 serotypes), echoviruses (28 serotypes) and other enteroviruses. Based on phylogenetic data, human enteroviruses are currently grouped into seven species (human enterovirus A–D and human rhinovirus A–C) encompassing more than 250 serologically distinct viruses. They can manifest themselves in a wide range of diseases, such as cutaneous, visceral, and neurological diseases. These viruses can be transmitted by nasal and throat secretions (saliva, sputum, or nasal mucus), blister fluid, or stool of infected individuals. The virus can bedetected in the stool and pharynx several days before the onset of the illness and continues to shed through the stool for several weeks.[3]

Even if clinical features are similar during HFMD, some specific aspects have been often associated with particular viruses. The rashes associated with CV-A16 usually appear as large vesicles. In EV-A71 infection, the rashes are petechial and/or papular, mainly on the trunk and limbs. Coxsackievirus A6 infection has a wide range of manifestations including severe or atypical HFMD, and nail shedding during the convalescence period. HFMD can cause severe complications including myoclonic seizure, tremor, nystagmus, brainstem encephalitis, and polio-like paralytic disease.

HISTORY

Hand, foot, and mouth disease can start with a low-grade fever, reduced appetite, and general, erythema, eventually rupturing and forming superficial ulcers with a grey-yellow base and erythematous rim. The exanthem can be macular, popular, or vesicular. The lesions are about 2mm to 6mm in size, are non-pruritic, and are typically not painful. They last about ten days, tend to rupture, and result in painless and shallow ulcers that do not leave a scar. The exanthem can involve the dorsum of the hand, feet, buttocks, legs, and arms. Oral lesions commonly involve buccal and tongue ulcers but may also involve the soft palate.

SIGNS AND SYMPTOMS

- Pain circumstances occur while swallowing.
- Stomachache.
- WHOLE BODY: Dehydration, Fatigue, Fever.
- SKIN: Rashes, Red spots, Blister.
- COMMON: Coughing, Headache, Irritability.[9]
- Oral pain.
- Ulcers appear on the oral mucosa.

Fig 1: Maculopapular Lesions on The Palms of The Patients With Hfmd.

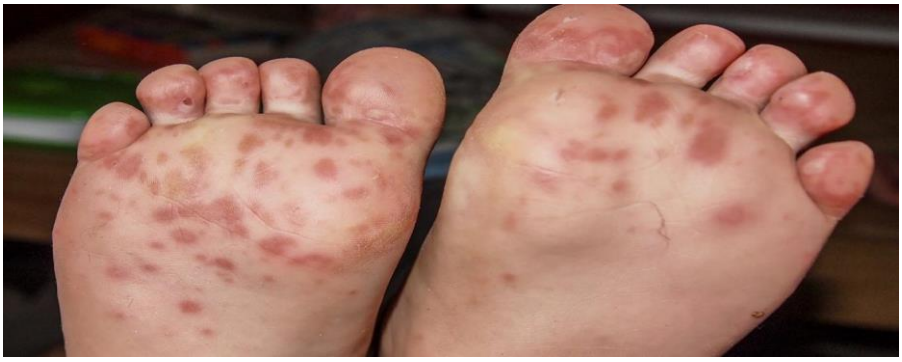

Fig 2: Maculopapular Lesions on Soles of Patient With Hfmd.

Risk Factors

1. Close contact with infected patient.
2. Attendance at a kindergarten/ child care center.
3. Residence in rural areas.
4. Overcrowding.
5. Poor hygiene.
6. Low socioeconomic status.

EPIDEMIOLOGY

HFMD epidemiology only receives attention in regions where the disease isendemic and several severe cases have occurred. The Western Pacific World Health Organization (WHO) Region is the best example. activated, and in some cases, notification of health authorities regarding disease has become mandatory. For example, in China, the country with the highest number of inhabitants and with one of the most advanced surveillance systems, HFMD has been categorized as a notifiable disease since 2008, and characteristics of infectious agents are continuously monitored.[13]

During the period from May 2008 to June 2014, a total of 10,717,283 HFMD cases were reported in China, with 3046 deaths and a fatality rate of 0.03%. Among survivors, morbidity increased from 37.6/100,000 in 2008 to 139.6/100,000 in 2013 and peaked in 2012 at 166.8/ 100,000. More than 90% of the cases were diagnosed in children < 5 years of age.

Mortality was higher among those ≤ 2 years old; 84.02% of the deaths occurred in thisage group, indicating that susceptibility and severity of HFMD are associated with age. Among other potentially associated factors, sex was not found to be associated with susceptibility but was found to be associated with disease severity.[4]

Infection rates are similar in males and females but males are more likely to develop symptoms, to have diffuse infections, and to need medical assistance diffuse infections and need medical assistance.

PATHOPHYSIOLOGY

This virus belongs to the Enterovirus genus, first isolated in 1948, in New York state by Dalldorf et al., who were investigating an outbreak of paralytic poliomyelitis in Coxsackie village. The virus is single-stranded RNA, surrounded by an icosahedral capsid made up of

proteins, size is 22 to 30nm, divided into 2 subgroups A & B. Coxsackie A contains 24 serotypes, while Coxsackie B has 6 serotypes.[8]

Spread in humans in the case of HFMD is through close personal contact like coughing, sneezing fomites, etc. by the shed virus from the intestine of the infected person or through the upper respiratory tract by the secretions or vesicle fluid of the diseased individual. Patients tend to be most infectious in the first week of the clinical condition, It is a benign illness resolving in 1- 2 weeks. After ingestion, the virus replicates in lymphoid tissue of the intestine & pharynx, spreads to regional lymph nodes, and then to multiple organs including CNS, heart, liver & skin.[6]

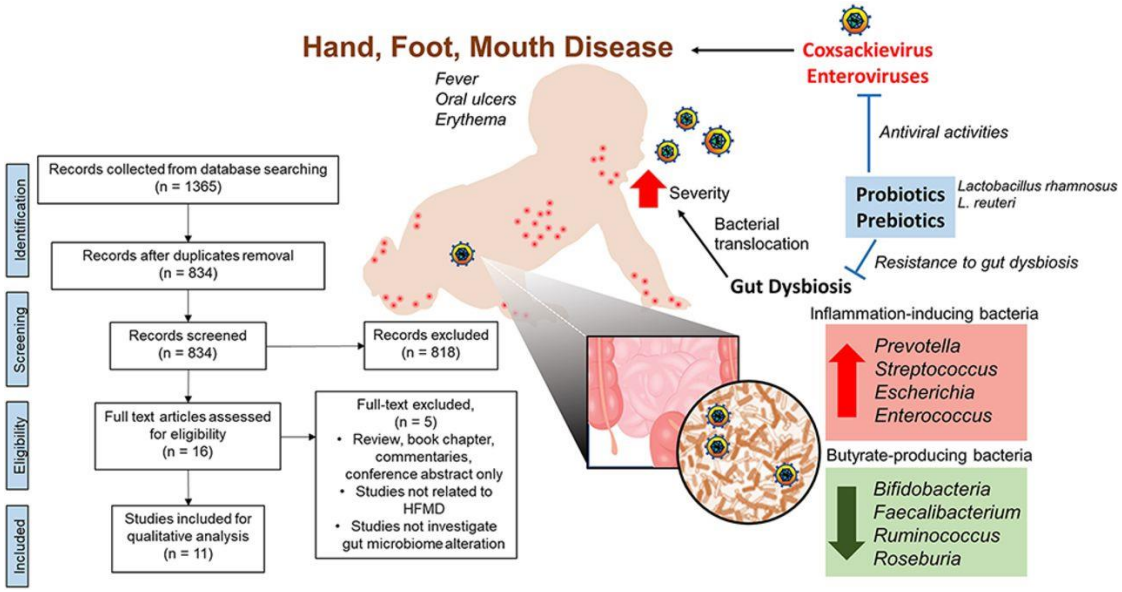

Fig 3: Pathophysiology of Hfmd.

CLINICAL FEATURES

Hand-foot-and-mouth disease is a clinical diagnosis based on the presentation of a low-grade fever with a maculopapular or papulovesicular rash on the hands and soles of the feet and painful oral ulcerations. If the diagnosis is unclear, serologic and polymerase chain reaction studies may be obtained to detect enterovirus or coxsackievirus.1,4,5,12 • Skin lesions are typically 2 mm to 6 mm in diameter, have an erythematous halo, and evolve into vesicles that rupture and leave painless shallow ulcersthat do not scar.[10]

• Oral anthems of painful ulcerations typically affect the posterior oral cavity, including the soft palate. Lesions may also affect the tongue and buccal mucosa, and pain may cause dehydration.

• Lesions resolve in seven to 10 days.

• Patients may have atypical skin lesions, including hemorrhagic or purpuric lesions; bullae and pustules; trunk, cheek, or genital involvement; palm and sole of the feet desquamation; and accentuation in areas of atopic dermatitis (eczema coxsackie).[5]

• The disease may be associated with delayed nail separation or horizontal nail ridges or grooves.

• Rare neurologic complications can occur such as aseptic meningitis, acute flaccid paralysis, and encephalomyelitis, especially with enterovirus.

• Other rare complications include pulmonary edema, pulmonary hemorrhage, and cardiorespiratory failure.

Clinical Manifestations

Some of the EV infections that can cause HFMD are asymptomatic. However, the true incidence of asymptomatic infections is not known. Few studies have assessed asymptomatic infections, and the studies that have been conducted have frequently used debatable methodology. Moreover, differences in the virulence of EVs can influence symptom and sign development. However, based on data collected during two prospective studies conducted during a large epidemic of EV-A71 infection, it was concluded that when this EV is circulating, approximately 30% of initially negative subjects seroconvert but do not have any clinical manifestations. This finding suggests that approximately one-third of infections remain asymptomatic.

Diagnosis

The differential diagnosis for HFMD should include conditions that present with maculopapular or vesicular rashes with or without oral lesions.

These conditions include.

• Erythema multiforme

• Herpangina

• Herpes simplex

• Herpes zoster

• Kawasaki disease

• Toxic epidermal necrolysis(TEN)

• Viral pharyngitis

• Rocky Mountain spotted fever.[12]

• Varicella zoster infection (chickenpox)

• Steven-Johnson syndrome

• Monkeypox - In the context of an ongoing outbreak, it becomes important to consider the difficulty in clinically differentiating between monkeypox and HFMD.[7]

Prognosis

The prognosis for most patients with hand, foot, and mouth disease is excellent. Most patients recover within a few weeks without any residual sequelae. Acute illness usually lasts 10 to 14 days, and the infection rarely recurs or persists. However, some patients with hand, foot, and mouth disease may develop serious complications, which include the following.

- Persistent stomatitis is associated with painful ulcers. The pain can be severe enough to limit food intake, and dehydration can result, especially in young children.

Complications

Pneumonia, myocarditis, pancreatitis, and pulmonary edema, as well as serositis involving other major organs, are rarely associated with HFMD. A large meta-analysis of children with HFMD suggested that lethargy, pneumo-edema/pneumorrhagia, seizures, dyspnoea, and coma were risk factors for death in HFMD. The case fatality rate associated with enterovirus 71 was found to be 1.7% in a systematic review and meta analysis.

Deterrence and Patient Education

Patient/parental education is paramount in reducing the transmission of HFMD among children and also between children and adults. Handwashing has been proven to be an effective strategy in the prevention of HFMD transmission. A community intervention study showed that intensive education on hand hygiene techniques led to an improvement in the personal hygiene of both parents and children. This subsequently reduced theincidence of HFMD in the study population. The parents should also be advised to keep the child away from immunosuppressed individuals due to the potential risk of serious illness.

Enhancing Healthcare Team Outcome

Cases of HFMD are on the rise, and clinicians need to know how to make the diagnosis. Because many recent cases have involved the brain, a neurological consult may be necessary. An interprofessional team that includes clinicians (MDs, DOs, NPs, or PAs), specialists (neurologist, pediatrician, internist, infectious disease expert), nursing staff, and a pharmacist should be involved. Clinicians will diagnose and initiate therapy and decide which referrals

may be necessary. Pharmacists can assist with medication management, perform medication reconciliation, and answer questions about the agents used. Nurses will coordinate activities with other interprofessional team members, help with patient examination, and counsel patients and/or parents. Everyone on the team must communicate openly with the rest of the care team to ensure the best care leading to optimal outcomes.

The outcomes for most patients with HFMD are excellent, with full recovery occurring within 7 to 21 days.

TREATMENT

- Main stay of treatment is supportive therapy, to control the temperature & hydration of the patient NSAIDs & acetaminophen for controlling the fever, fluid replacement to keep the patient well hydrated.[11]
- Liquid ibuprofen will be used as gargle to ease the pain in the throat.
- Novel agents –molecular decoys, translational inhibitors, receptor antagonists, replication inhibitors play a vital role in the management of the viral infection case.
- Pleconaril –anti picornoviral agent plays an important role.
- Hand hygiene is the main stay of prevention.

Vaccines

- Strain-specific inactivated whole virus aluminum adjuvant vaccine is available in China and approved for widespread use –EV71C4a vaccine showed an overall 94.7% efficacy with protection for 2 years.
- VLPs vaccine, DNA vaccine, peptide vaccine, and subunit vaccines are in various stages of clinical trials.[2]

CONCLUSION

Hand, foot and mouth disease is a self limiting viral infection, prevented by proper hygienic precaution, for which each one of us are responsible. It has been clarified that HFMD can be associated with severe complications, leading to neurological sequelae, and rarely to death. Vaccines able to confer protection against in a country have been developed.

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