

Current status of drug treatment for hand foot mouth disease

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Abstract. Hand, foot, and mouth disease (HFMD) is an infectious disease caused by the intestinal RNA virus. Hand, foot, and mouth disease can occur every season, with no significant difference in specificity. However, the more frequent season of onset is spring and summer, with April to September as the main month of onset. Coastal areas are relatively popular areas of incidence. HFMD is mainly characterized by herpes with different sizes and clinical manifestations, such as in the hands, feet, and mouth. This article categorizes drugs into two categories: antiviral drugs and antiviral prevention. In describing antiviral drugs, they are classified them into traditional Chinese medicine and non-traditional Chinese medicine. At the same time, the two most effective and commonly used drugs or methods are summarized for preventing HFMD, namely the EV-71 virus vaccine for HFMD, and the washable hand sanitizer that prevents HFMD by blocking the transmission path of the virus. A comprehensive description and summary of the current treatment methods and drugs for combating and treating HFMD. This article provides a comprehensive description of different drugs by elaborating on their advantages and therapeutic principles, combined with their related pharmacological effects.

Keywords: HFMD, Ribavirin, Interferon Alpha 2b Spray, Xiyanping, Vaccine.

1. Introduction

HFMD is a mild infectious viral infection common among young children. HFMD is highly infectious, fast in transmission and wide in approach, and can cause a wide range of epidemics in a short time. The incidence rate will show an explosive growth trend, which has become a major difficulty and hot spot of widespread concern in the whole society [1]. The symptoms are mainly persistent fever, accompanied by sporadic herpes in the mouth, hands and feet, which is relatively high in children under the age of 5. The main route of transmission of HFMD is respiration tract infections. The general preventive measures are to strengthen the establishment of hygiene awareness, such as washing hands before meals. Statistical data show that very few children with severe hand, foot, and mouth disease progress rapidly, leading to critical complications such as meningoencephalitis, myocarditis, and neurogenic pulmonary oedema, endangering the lives of children. The actual infection rate of enterovirus in children aged 5 years and under was 27.74% on average, and the incidence rate of HFMD was 5.80% on average. HFMD has also caused certain economic impacts, and once infected, families of HFMD patients will face certain economic expenses. In 2018, the average cost of non-hospitalized cases was 156.92 ±

175.80 yuan/case: among hospitalized cases, the average cost of mild cases was 2247.97=2390.27 yuan/case, and the average cost of severe cases was 14449.45 ± 9826.90 yuan/case, The average cost of death cases is 147-17 million per case. The annual economic loss caused by HFMD is 53-120 million [2].

The main pathogens of HFMD are Coxsackie virus A and enterovirus 71 (EV-A71). Although the majority of HFMD cases are mild and have certain limitations, it is reported that EV-A71-related HFMD has neurological complications [3]. However, monovalent vaccines targeting the EV-A71 virus currently only exist in the Chinese market [3, 4]. EV-71 virus is a non-envelope-positive single-stranded RNA (SSRNA) virus. 5% of its genome 5' - UTR is covered by VPg proteins and contains an internal ribosome entry site (IRES) and several clover structures that regulate viral RNA replication and translation [5, 6]. The coxsackie virus that causes hand, foot, and mouth disease includes types 16, 4, 5, 9, and 10 of the coxsackie virus group A, of which the most common is type 16.

Currently, the treatment of HFMD disease mainly focuses on symptomatic and supportive treatment. Currently, there are few specific antiviral drugs, and most of the treatment is through the use of broad-spectrum antiviral drugs., Early use of interferon as a broad-spectrum antiviral drug has significant therapeutic effects [7]. However, interferon is specific in combating enteroviruses and has a high relapse rate after drug withdrawal [8]. The efficacy of interferon alone is not satisfactory, and it has no direct effect on symptoms such as high fever, inflammation, and oral ulcers in HFMD disease. Currently, there are much traditional Chinese medicine and traditional Chinese medicine preparations combined with interferon treatment methods, with significant therapeutic effects. For example, Kangfuxin liquid combined with interferon treatment is both a causal and symptomatic treatment [9]. Then, here are some examples of drugs that protect against the HFMD virus.

2. Antiviral drugs

2.1. Non traditional Chinese medicine

2.1.1. Ribavirin. Ribavirin spray can be used to treat blisters on the fourth day of HFMD, a viral infectious disease caused by RNA virus infection. For antivirals, one option is ribavirin, also known as riboside tourism, which is a broad-spectrum antiviral. However, it is important to note that ribavirin has a number of side effects, especially when administered intravenously, which can produce reproductive toxicity and hematological toxicity and should be considered when using ribavirin in children [10].

Ribavirin is a commonly used antiviral drug that acts as an antiviral by inhibiting inosine monophosphate dehydrogenase, preventing guanosine resynthesis, inhibiting viral replication, indirectly controlling cellular immunity, and protecting virus-infected cells. Ribavirin has shown antiviral activity against a variety of respiratory viruses and enteroviruses. Using poliovirus as a model, it was found that ribavirin can act on the genome of RNA viruses and induce lethal mutagenesis. Poliovirus enters the body's central nervous system through oral transmission, impairs motor function in the spinal cord and causes muscle function to decrease to the point of loss, killing the body. Ribavirin primarily inhibits the RNA-dependent RNA polymerase of poliovirus so that poliovirus can induce mutations to generate new RNA templates and act as an antiviral. Coxsackie virus (CV) belongs to RNA viruses, such as CVB3 can induce direct cell damage, and then cause target organ tissue damage and dysfunction through the interaction of human inflammatory response to CVB3 infection and cell death. Ribavirin inhibits viral uptake by binding to the capsid of the virus, thereby inhibiting viral replication and reducing its transmission. CVA10 can also cause HFMD. Ribavirin was found to be effective in the treatment of HFMD, significantly inhibiting CVA10 with an in vitro inhibition rate of 32% and in vivo protection rate of 60%, indicating that ribavirin is able to inhibit CVB replication [11].

Ribavirin is rapidly absorbed after oral administration (maximum concentration time =1.5 hours), followed by rapid distribution and extended elimination phases. Absorption in the proximal small intestine is active via a concentrated N1 sodium-dependent nucleoside transporter. Ribavirin appears to be widely absorbed. However, absolute bioavailability is around 50%, presumably due to primary

metabolism. Because ribavirin is distributed via ES- nucleoside transporters to non-plasma (cellular) compartments, its surface distribution volume is wide (about 2000 L). The ribavirin does not bind to plasma proteins. After multiple doses, there is a large build-up in the plasma that takes about four weeks to stabilize. The multi-dose half-life is approximately 298 hours due to the slow elimination of ribavirin from the non-plasma compartment. The pharmacokinetic properties of ribavirin in particular populations, the effects of food on the pharmacokinetics of ribavirin, and potential interactions between ribavirin and other preparations are also reviewed.

2.1.2. Interferon alpha 2b spray. Interferon α is an important immunoprotective cytokine that can only effectively bind to cell surface receptors, express antiviral proteins, inhibit virus replication, and prevent the virus from invading normal cells. It can also enhance cellular immunity and promote the proliferation of cytotoxic T lymphocytes, with significant viral clearance.

Recombinant human interferon is used in children with HFMD α - The clinical efficacy of 2b aerosol inhalation treatment is significant [12]. Administration of recombinant human interferon to children with HFMD α - After 2b aerosol inhalation therapy, the drug can play a protective role in the process of enterovirus infection, directly clearing the invading RNA virus, and does not require the joint involvement of the immune system, resulting in no drug resistance. The spray inhalation of interferon also avoids various symptoms such as chills, muscle soreness, and fever caused by intramuscular or subcutaneous injection [12].

2.2. Traditional Chinese medicine

2.2.1. Xiyanning. Xiyanning is produced by using modern technology to extract andrographolide from the entire leaves of the plant *Andrographis*, and through a unique sulfonation patented process.

A water-soluble traditional Chinese medicine injection, which changes the structure of andrographolide components themselves and enhances their pharmacological effects due to structural changes [13]. The drug concentration in the blood is higher, and it can well penetrate viral cells, occupy the binding sites of viral replication DNA and protein, and prevent protein from wrapping DNA fragments, making the virus unable to replicate, thereby inhibiting or killing the virus. Xiyanning has pharmacological effects such as antiviral, enhancing immunity, clearing heat, and anti-inflammatory, which is beneficial for disease recovery. The study used a control method to compare the effective rates of Xiyanning and ribavirin in the treatment of patients with non-severe HFMD. The effective rate of Xiyanning was 94.28%, while the effective rate of ribavirin was 70% [14]. And this result has statistical significance after statistical verification. In addition, in the study, patients treated with Xiyanning had shorter fever relief time, rash resolution time, stomatitis healing time, and hospital stay than those in the control group treated with ribavirin [14].

2.2.2. Treatment of HFMD with combination of traditional Chinese medicine. For the treatment of HFMD, conservative treatment is mostly used in medicine. However, compared with Western medicine, which has many adverse reactions to the human body, Chinese medicine is very popular among patients for its mild medicinal properties and low medicinal cost. In 2020, 70 children with HFMD of damp heat and steaming type were admitted to Luxi County Maternal and Child Health Hospital in Jiangxi Province, China, which proved the value of Qingwen Baidu decoction combined with traditional Chinese medicine fumigation for HFMD of damp heat steaming type. All patients and their family members excluded special cases. The control group chose the treatment method of traditional Chinese medicine fumigation and washing, and observed that Qingwenbaidu Decoction combined with traditional Chinese medicine fumigation and washing was used for treatment. consistent. After careful comparison of the time of the disease's disappearance, immune function and other conditions, the researchers concluded that clinical TCM treatment of HFMD should choose the method of dispelling dampness, clearing qi, clearing away heat and detoxification; Qingwenbaidu drink with fire function. They can be used in combination with western medicine to alleviate the damage to the human body

caused by the excessive therapeutic effect of western medicine [15]. Similarly, from 2018 to 2019, Huangpu People's Hospital of Zhongshan City, Guangdong Province, China adopted 78 patients with HFMD, treated with western medicine ribavirin as a control, and compared Yinqiao Haoqin Decoction combined with traditional Chinese medicine acupoint application in the observation group. Keeping other observations on the treatment effects of the two groups and the safety of the medication, the researchers concluded through comparison that the latter traditional Chinese medicine therapy makes the medication safer and the time for the disease to subside will be significantly shortened (for example, the patient's fever will go down faster, Herpes dissipates faster), has more definite curative effect and faster recovery of patients [16]. Xiyanping injection was also widely used in the medical field for HFMD. The fumigation treatment in traditional Chinese medicine can also fit the treatment concept of viral infection. Yingtan Hospital of Traditional Chinese Medicine, Jiangxi Province, China, from September 2014 to 2015 In February 2010, 40 children with HFMD were randomly selected. The experimental group and the control group had the same number of people and the age range was 1.8 to 2.9 years old. The experiment was carried out after the researchers confirmed that there was no statistically significant error. All variables such as the basic treatment course and drug dosage of the control group and the experimental group are the same, and the experimental group uses the medicine fumigation and washing made of various medicinal materials once a day. The result is that all the data of the experimental group are superior to those of the control group. It is concluded that the treatment of traditional Chinese medicine has been developed since ancient times and has gradually matured. Many experiments and real data have proved that the combination of traditional Chinese medicine and Western medicine is handicap. Mouth virus and even more other types of viruses have good curative effects, which also suggests that medical workers can more vigorously promote the rational use of traditional Chinese medicine in the course of treatment [17].

3. Medications for preventing hand, foot, and mouth disease

3.1. TJAB1099

EV-71 virus is mainly transmitted orally through direct contact with oropharyngeal secretions and faeces through contaminated objects. Therefore, blocking this route of transmission is an effective way to prevent the spread of the virus. Although patients and non-patients usually have certain isolation measures. Routine methods such as isolation, ventilation, and surface disinfection are used to control the spread of the virus. However, the disinfection effect of these methods is very limited, and EV71 is mainly transmitted through direct contact type direct transmission. Vulnerable populations, such as children, have the habit of not washing their hands and sucking their fingers, which is the most important reason for the spread of the virus among children. Therefore, hand disinfection is the most direct and effective method to block the spread of EV71. EV71 is a non-envelope virus. Eliminating a series of EV-71 viruses targeting the hands can effectively inhibit the spread of the HFMD virus.

However, due to the high stability of EV71, the inactivation effect of traditional disinfectants such as alcohol on EV71 is not ideal. A new pyridyl imidazol idone compound (TJAB1099) can specifically inhibit the replication of EV-71 in vitro. However, TJAB1099 is insoluble in water, resulting in extremely low bioavailability, and is not suitable for oral absorption [18].

A washing-free gel containing TJAB1099 was developed because Carbopol semi-solid gel is easy to dissolve with TJAB1099 in ethanol, and it will quickly liquefy after being heated by hand contact. This makes the development of TJAB1009 wash-free gel feasible [18].

3.2. vVaccine

The research and development of the EV71 vaccine mainly include inactivated whole virus vaccine, attenuated live vaccine, virus-like particle vaccine, and DNA vaccine. Currently, three companies in China, including the Institute of Medical Biology of the Chinese Academy of Sciences, Beijing Kexing Biotechnology Co., Ltd., and China Biotechnology Group Wuhan Institute of Biological Products, have approved the listing of EV71 vaccines.

The meta-analysis results of the EV71 vaccine have been verified in the EV71 vaccine-vaccinated population [19]. The whole genome microarray was used to detect the changes in the transcriptome of peripheral blood mononuclear cell during the initial immune response and re-response of the new EV71 vaccine. It was found that the initial immune response could activate the type I interferon and antiviral response pathway, while a stronger type I interferon and antiviral response, inflammatory response, and humoral immune response was only observed during the re response [19]. In some studies, all healthy children aged 6 to 59 months who were vaccinated with the EV-A71 inactivated vaccine in the vaccination clinics in 89 counties (cities, districts) of Zhejiang Province from April 2016 to March 2018 were selected as the study subjects. The local and systemic adverse reactions of the vaccinators were collected through observation within 30 minutes of the vaccination site, follow-up within 3 days, and 4 to 30 days of vaccination, respectively. A total of 71663 doses of EV-A71 vaccine were administered, with no significant difference between the doses administered to boys and girls; The 6 to 11, 12 to 23, and 24- to 59-month-old groups were vaccinated with 13707, 32639, and 25317 doses, respectively. The incidence of adverse reactions was 0.33% (239 dose times), 1.58% (1133 dose times), and 0.34% (244 dose times) within 30 minutes, 3 days, and 4 to 30 days after inoculation, respectively. A total of 1372 dose times of adverse reactions occurred within 3 days, with an incidence of 1.91%. Among them, 539 dose times of first-level adverse reactions occurred, 677 dose times of second-level adverse reactions occurred, and 156 dose times of third-level adverse reactions occurred. There were no fourth-level adverse reactions. Among local adverse reactions, redness, induration, and pruritus are more common, with an incidence of 0.05% (39 dose times), 0.02% (16 dose times), and 0.02% (12 dose times), respectively. Among systemic adverse reactions, fever is the most common, with an incidence of 1.19% (856 dose times), followed by diarrhoea and decreased appetite, with an incidence of 0.15% (104 dose times), and 0.13% (90 dose times), respectively [20]. The adverse reactions after vaccination with the EV-A71 vaccine are mostly mild and common, with no rare adverse reactions found.

4. Conclusion

Drugs for HFMD is actually a lot. Currently, there are no specific drugs to treat HFMD-related viruses. Generally, prevention of HFMD is implemented through both vaccination and attention to personal hygiene to block the transmission path. However, at this stage, only the EV71 vaccine is approved by the CFDA (China Food and Drug Administration). There are more than 20 enteroviruses that can induce HFMD, so the EV71 vaccine cannot completely prevent the occurrence of hand, foot, and mouth disease. For antiviral drugs that inhibit viral replication or destroy viral proteins, broad-spectrum antiviral drugs, such as ribavirin, are commonly used in clinical practice. Ribavirin can develop resistance, so it is necessary to control the dosage of each intake. The main drugs for HFMD that improve the immune system and strengthen resistance are interferon. In China, doctors will use traditional Chinese medicine or traditional Chinese medicine combined with antiviral drugs to treat HFMD, which has a significant role in antiviral and immune enhancement. With the invasion of hand, foot, and mouth disease virus into the human body and its auxiliary mechanisms gradually being thoroughly studied, inhibiting the replication of HFMD virus has become an important idea in the research of HFMD-specific drugs. It is believed that more specific drugs and vaccines related to HFMD will be developed in the future, and people need to maintain our expectations.

References

- [1] Liu, Z., "The "Three in One" Certification and Accreditation of Testing Laboratories" . . Res. Explor. Lab.,32(5) : 219 – -221 (2013) . .
- [2] Chen,X.,yu,X. wang,G . . "Analysis of Non conformities in the External Audit of the Laboratory Quality Management System of Disease Control and Prevention Institutions in Zhejiang Province".Chin.J.Health.Lab.Tec, 25(4): 598 – -599 (2015).

- [3] Wang,X. “study on the burden of hand,foot, and mouth disease and the effectiveness evaluation of THE EV-71 vaccine program in BEIJING”[D].Chinese Center for Disease Control and Prevention,10:130 (2019).
- [4] Solomon T, Lewthwaite P, Perera D, et al. “Virology, epidemiology,pathogenesis,and control of enterovirus 71”.*Lancet Infect Dis.*10(11):778-790 (2010).
- [5] Thompson SR, Sarnow P. “Enterovirus 71 contains a type I IRES element that functions when eukaryotic initiation factor eIF4G isCleaved”. *Virology.* 10;315(1):259–266 (2003).
- [6] Kok CC, Phuektes P, Bek E,. “Modification of the untranslatedregions of human enterovirus 71 impairs growth in a cell-specificManner”. *J Virol.* 86(1):542–552 (2012).
- [7] National Health Commission of the People's Republic of China.”Diagnosis and Treatment Guidelines for Hand, Foot, and Mouth Disease”.*Nation. Health Commis. Chin.*39(4):257-263 (2018).
- [8] yin,M.”The clinical effect of combination of Reduning and interferon in the treatment of hand, foot,and mouth disease in children”. *Clinical Med. Res. Pract.*5(34):147-149 (2020).
- [9] Ji,T.,Feng,X.,Zheng,L.”Meta analysis of Kangfuxin liquid combined with interferon in the treatment of hand, foot, and mouth disease in children”.*Modern Med. Health*,39(04):605-609 (2013).
- [10] Weeramanthri TS, Dawkins HJS, Baynam G,et al.”Frontiers in Public Health”.*Precision Public Health.*6:121., 17 (2021).
- [11] Hu,Y.,Liu,L.,Liu,J.”Research progress on the pharmacological effects of ribavirin”. *J. Jilin Medl Colleg.*43(03):208-212 (2022).
- [12] Chen,H.,chen,X.,zhou,J.”Recombinant human interferon α - Effect of 2b spray on immune function of children with hand foot mouth disease”. *Chin. J. Hospital Infect.* 29(10): 1562 - 1566 (2019).
- [13] Zhao,C.,zhao,S. “Epidemic situation and response strategies of hand, foot, and mouth disease”.*Chin. J. Pract. Pediatrics.*24(6):419 (2019).
- [14] Liu,F. “The therapeutic effect of total sulfonated andrographolide (Xiyanping injection) on pediatric hand, foot, and mouth disease“. *Capital Med.* 21(04):36 (2014).
- [15] Liu,W.”Clinical Effect and Safety Analysis of Qingwen Baidu Decoction Combined with Fumigation and Washing with Traditional Chinese Medicine in the Treatment of Damp-heat and Steaming Type of Hand-foot-mouth Disease in Children”. *Guide Chin. Med.*21(03):132-135(2013).
- [16] Wu,D. “Observation on the therapeutic effect of Yinqiao Haoqin decoction combined with traditional Chinese medicine acupoint application on children with hand, foot, and mouth disease”. *Shenzhen J. Integr. Tradit. Chin. West. Med.*30(10):55-56(2020).
- [17] Chen,J.”Observation on the effect of Xiyanping injection combined with traditional Chinese medicine fumigation and washing in the treatment of hand, foot, and mouth disease in children”. *Contemp. Med.* 22(36):188-189(2016).
- [18] Ma H Q,Wang Y,Mao Y H,et al.“ The inactivation of the non - enveloped enterovirus 71 (EV71) by a novel disinfectant gel formulation for topical use”. *Drug Dev Ind Pharm.*45 (3) : 506-513(2019).
- [19] Zhao,J. “System Biology Study on the Immune Mechanism of EV71 Whole Virus Inactivated Vaccine”.*Jilin University.*(08):112,(2016).
- [20] Luo Y,Fu J,Pan X J, et al. “Post-marketing safety analysis of inactivated enterovirus A71 vaccines”. *Chin. J prev. med.*,53(3).(2019).