MINI-NARRATIVE REVIEW

'Tomato flu' a new epidemic in India: Virology, epidemiology, and clinical features

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Abstract

This article aims to highlight the current update on the 'tomato flu' outbreak in India. Recently there was an outbreak of a new illness in some parts of India. The disease was very contagious and it manifested with a rash mainly noticed in children younger than nine years. The rash was very painful and blisters were the size of small tomatoes, hence it was termed 'tomato flu'. A detailed literature review was performed on the virology, replication, epidemiology, and clinical features of this disease. The current outbreak was compared with similar other diseases of the past. The affected children exhibited severe rash in the palms, soles, oral cavity, and other body parts. They developed febrile illness with a sore throat, and myalgia followed by blisters on the tongue, gums, and cheeks. The affected children did not develop any complications leading to death. The therapy involved mainly symptomatic, supportive treatment with isolation and maintaining hygienic practices. The causative agent was identified to be Coxsackievirus A16, an RNA virus belonging to the family, Picornaviridae. We conclude that the recent Indian epidemic of this disease might be due to a new variant of Coxsackievirus A16 actually causing HFMD.

Keywords: Blisters, Clinical features, Coxsackievirus A16, Hand foot and mouth disease, Rash, 'Tomato flu', CA-16, HFMD
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1. Introduction

Hand, foot and mouth disease (HFMD) is a typically benign viral infection of the childhood and the disease was first described in 1948. Coxsackievirus A16 (CV-A16) and human enterovirus 71 (EV-A71) are the major pathogens responsible for HFMD. As the infection was deemed a mild viral infection, associated with self-limiting clinical features that resolved within 5 to 7 days, HFMD did not receive a lot of attention for a long time [1]. However, over the past years, HFMD has received more attention due to the increasing evidence that there is a large number of HFMD cases that have atypical presentations.

In May of 2022, an infectious viral disease caused by an unknown etiologic agent emerged in India, in the Kollam district of Kerala. This infection presented with usual symptoms of flu, such as fever, fatigue and body ache. What set it apart was the manifestation of red, painful blisters that grew to the size of a tomato, hence conferring the name 'Tomato Flu' (Fig. 1). Much like the typical HFMD, this disease was rapidly spreading among young children. As of now, it has been identified that 'Tomato Flu' is caused by CV-A16. Hence, 'Tomato Flu' is now considered a misnomer and the clinical features of this disease are discussed as an atypical presentation of HFMD [2].

In this mini-review, the recent outbreak of HFMD in India – notoriously termed as 'Tomato Flu' – will be discussed, with emphasis on virology, epidemiology and clinical features.

2. Materials and methods

A detailed literature review was performed on the search terms "tomato flu", "hand foot and mouth disease", "HFMD", "Coxsackievirus A 16", "blisters", "rash", "transmission",

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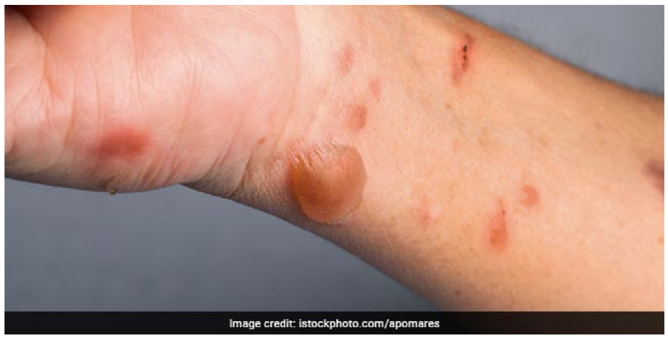

FIG. 1. Vesiculobullous blister in a patient with 'tomato flu' (image credit: istockphoto. com/apomares).

"replication", "virulence", "prevention", "treatment" and "antiviral drugs". Search engines/data bases from EMBASE, PMC, PubMed and Google Scholar were used for this study. A total of 165 articles found in different data bases were analyzed. The inclusion criteria for this study were: (a) articles written in English; (b) original articles, review articles and case reports published between the period January 1985 to October 2022. Exclusion criteria for the articles were applied based on, (a) articles with insufficient data; (b) studies prior to January 1985, (c) outdated data; Necessary information were also received from gray literature.

2.1. Recent epidemic in India

The recent epidemic of this new viral disease, termed 'tomato flu', was first noticed in Kollam district, Kerala on the 6th of May 2022. The disease had later spread to other parts of Kerala, including Anchal, Aryankavu, and Neduvathur. According to Lancet Respiratory Medicine, 82 cases were detected in Kerala from children under the age of five by late July 2022. The disease has now spread to other states in the North East of India including Tamil Nadu and Odisha [3]. In these states an additional 26 cases have been reported, where children up to 9 years of age have been infected. It was speculated that the disease could be an after effect of chikungunya or dengue fever as the primary symptoms seen were high fever, rashes and intense pain in joints. The affected children have also reported having experienced rash in the body, fatigue, nausea, vomiting, diarrhea, fever, dehydration, swelling of joints, body aches, and common influenza like symptoms. However, the main symptom of this disease is the eruption of blisters that start as small, red spots resembling the vegetable tomato as they enlarge, and hence is where the name 'tomato flu' has emerged.

To investigate this disease, molecular and serological tests were performed in order to rule out dengue fever, chikungunya, zika virus, varicella zoster virus, and herpes, and upon ruling out these illnesses a diagnosis of 'tomato flu' was made [4]. Although the disease is endemic to India, 2 cases were identified in the United Kingdom soon after the family returned from holiday in Kerala in May 2022. Following this, in the United Kingdom, at a national reference laboratory, Porton Down, Salisbury, polymerase chain reaction was performed for enteroviruses and monkeypox. Further sequencing at another national reference laboratory, UKHSA-Colindale led to the identification of CV-A16 serotype as the main causative agent of the disease. CV-A16 is a common cause of HFMD, a contagious viral disease which usually affects infants and children younger than 5 years. Hence, the term 'tomato flu' is now considered as a misnomer and is no longer used, as HFMD is a well-established disease [5].

It is noteworthy that the disease can be very painful in spite of no major complications or records of death with the new variant. However, due to its contagious nature, swift and adequate preventive measures were enforced by the Health Department of Kerala Government to reduce the dissemination of the disease in the community. The public is advised to maintain proper hygiene and sanitization as well as to avoid sharing the belongings of an infected person with others. Furthermore, the government emphasizes on isolation for 5 to 7 days following the onset of symptoms [6].

2.2. Virology of Coxsackievirus A16

Coxsackievirus A16 (CV-A16) is one of the major etiologic causes of HFMD. It is a member of *Human enterovirus A* (HEV-A) species of the *Enterovirus* genus of the *Picornaviridae* family. CV-A16 is a single-stranded, positive sense, polyadenylated RNA virus of approximately 7400 bases with an icosahedral symmetry structure [7]. The genome, as like other enteroviruses, consists of three types of regions; non-coding regions, a structural region and a non-structural region. The reading frame (structural and non-structural regions) encodes a large polyprotein precursor, which is subsequently processed into structural protein P1 and non-structural proteins P2 and P3. P1 can be processed by a virus-encoded proteinase, which results in viral capsid subunit proteins VP0, VP1 and VP3, VP0 can be further cleaved to yield VP2 and VP4. VP1, VP2 and VP3 lie on the outer part of the capsid while VP4 is situated on the inner

part. The neutralization epitopes mainly reside on VP1 [8]. The non-structural regions P2 and P3 includes 2A, 2B, 2C, 3A, 3B, 3C and 3D which are replication proteins. The coding region that encodes large polyprotein precursor is flanked by 5′ and 3′ untranslated regions (5′UTR and 3′UTR). The 5′UTR contains approximately 740 nucleotides; they consist of sequences that control genome replication and translation. The 3′UTR contains a polyadenine tail which is essential for virus infectivity.

CV-A16 is a non-enveloped, icosahedral particle where the external portion of the icosahedral capsid comprises 60 copies of VP1, 2 and 3 while their N-terminal extensions and VP4 line the interior. An electron micrograph of the virus particles was shown in (Fig. 2).

2.3. Replication of the virus

Humans are the only known natural host for CV-A16 as of yet. It is generally believed that specific cellular receptors determine the host range specificity and tissue tropism for most animal viruses [9]. Human scavenger receptor class B, member 2 (hSCARB2) has been demonstrated to be a candidate cellular receptor for CV-A16. In a study where a murine model of CV-A16 infection was developed and characterized skeletal muscle was indicated to be the major site of early virus replication whereas brain was suggested to be the site for spread and replication at relatively late stage of infection. However, another study confirmed that CV-A16 had tropism to lung and brain tissues rather than to muscle tissues in nasally infected hSCARB2 transgenic mice [10].

When the virus enters a permissive host cell, the genome first serves as a template for translation producing the viral polyprotein, it then becomes a template for replication. 5′UTR is fundamentally required for these functions, specifically the internal ribosome entry sites (IRESs), occupying most of the 5′UTR, are involved in initiation of translation whereas the 5′-terminal cloverleaf structure is closely related with viral replication. The exact mechanism of viral replication of CV-A16 has not been well-studied, however, a study in a neonatal mouse model determined that 5′UTR of CV-A16 is crucial for virus replication and its virulence [11].

Since the exact mechanism of viral replication of CV-A16 is unknown, the following text elaborates the viral replication of enteroviruses. The enterovirus replication cycle is initiated when it binds to a receptor. This receptor binds at a depression in the capsid called the canyon, which surrounds the fivefold axis of symmetry. The virus is then internalized and the viral RNA is released into the cytoplasm which first serves as a template for translation producing the polyprotein [12]. The polyprotein is proteolytically processed by the viral proteases $2A^{pro}$ and $3C^{pro}$ to release the structural and non-structural viral proteins and some stable precursors. The viral proteases also cleave cellular targets in order to optimize the environment for viral proliferation and to suppress innate antiviral responses. The non-structural proteins, P2 and P3 mediate the replication of the viral genome. RNA genome replication is initiated by uridylation of the protein primer VPg by the viral RNA-dependent RNA polymerase $3D^{pol}$ using secondary RNA structure in the viral genome called cis-acting replication element (Cre) as a template [13]. VPg is then elongated by $3D^{pol}$ to produce a negative-stranded intermediate which in turn is used as a template for synthesis of positive-stranded RNA molecules. Positive-stranded RNA molecules can then either enter another round of translation and replication or they can be packaged into capsids to produce infectious virus particles. These new virus particles are then released upon cell lysis and through several non-lytic mechanisms (Fig. 3).

2.4. Virulence of EA-71 and CA-16

CV-A16 was identified as the causative organism of the recent outbreak of ‘tomato flu,’ which is generally self-limiting and less fatal. However, HFMD with EV-A71 is attributed to a more

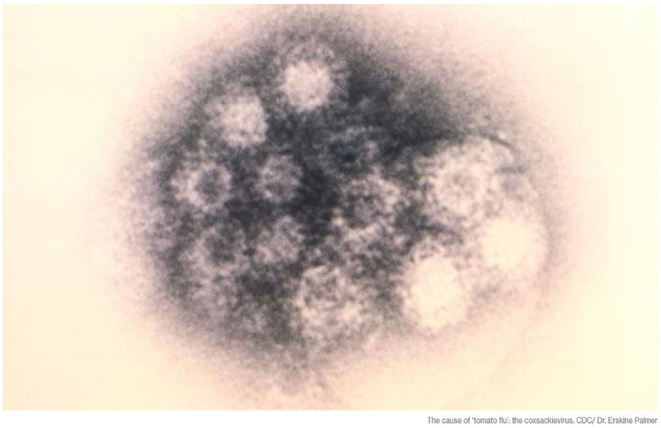

FIG. 2. Electron micrograph of ‘tomato flu’ agent, the Coxsackievirus (image credit: CDC/Dr. Erskine Palmer).

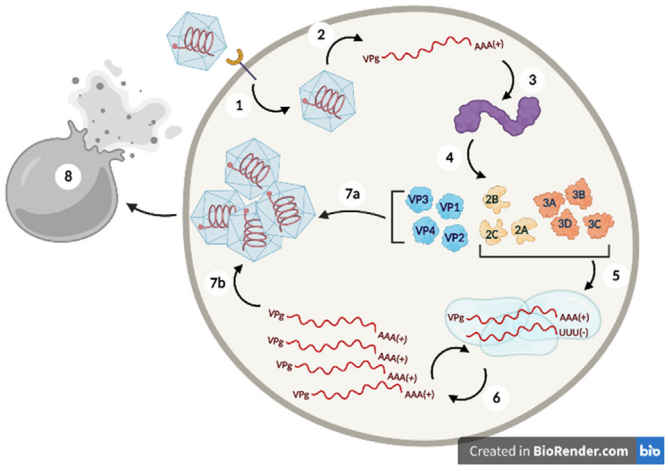

FIG. 3. A schematic diagram of the viral replication process The virus is taken up into the cell when the receptor binds to the canyon of the virus (1). The viral RNA is released into the cytoplasm (2), this serves as a template for translation which produces the polyprotein (3). The polyprotein undergoes proteolytic processing to release structural and non-structural viral proteins which are further processed to result in capsid proteins and replication proteins respectively (4). The viral replication proteins mediate the replication of the viral RNA (5). This produces a negative stranded intermediate that is used as a template for synthesis of positive stranded RNA molecules which can also undergo another round of translation (6). The capsid proteins form the capsid of the virus (7a) into which the positive stranded RNA are packaged into (7b) forming the infectious viral particles. These new virus particles are released upon cell lysis (8).

severe disease progression. In a comparative study done among 177 EV-A71 and 64 CV-A16 patients during the enterovirus epidemic in Taiwan, only 6.3% of CV-A16 infections developed into aseptic meningitis [14]. However, an alarming 32% of EV-A71 cases resulted in aseptic meningitis, encephalitis, polio-like syndrome, encephalomyelitis and fatal pulmonary edema.

The non-structural (NS) proteins of CV-A16 produced by cleaving P2 and P3 are known to be involved in the translation, replication and overtaking of the host cell. Meanwhile, the capsid proteins by cleaving P1 play a significant role in the cellular entry and uncoating of the genetic material. Subsequently, they are considered potential targets for the development of antivirals [15].

Coxsackie viruses are associated with a multitude of diseases. Both A and B types of CV-A16 are usually known for causing non-specific upper respiratory tract infection, febrile rashes and aseptic meningitis. Furthermore, CV-A are known to have a particular propensity for skin and mucous membranes. The pathogenesis of these viruses depends on specific virus-receptor interactions which determines where the primary infection arises from. In addition, it also contributes to the spread of the infection to other organs during the post-viremic stage [16].

In order to cause a successful infection there are few factors that play vital roles. These include the permissiveness of the target cell to viral replication and the susceptibility of the target cell to the virus, which is determined by the presence of appropriate viral receptors on the cell surface. One such receptor is the Human scavenger receptor class B member 2 (hSCARB2) that is utilized by EV-A71 and CV-A16, which is present on various cells including neuronal glial cells [17].

RNA dependent RNA polymerase (RdRp) is an essential enzyme for the replication of single stranded RNA in the picornavirus genome to which EV-A71 and CV-A16 belong. RdRp lacks proofreading abilities which contributes to the high mutation rates in these RNA viruses. Subsequently, many studies have identified varieties of mutations that lead to the formation of new proteins which contribute to adapted viral replication, survival and virulence of EV-A71.

One such example is the change of VP2 amino acid change at position 149 from lysine (K) to methionine (M) ($VP2^{K149M}$) which is associated with increase in RNA accumulation, viral cytotoxicity and uncoating in neuronal cells of mice and also increased mouse lethality in vivo. An additional finding identified $VP1^{145Q}$ as a crucial factor for increased infectivity in human airways. $VP1^{D31G}$ mutation was also found to augment EV-A71 entry into neuroblastoma, increase viral growth rate in human neuronal cells and it had a higher proportion of fatal patients among the viral population than in HFMD [18].

EV-A71's structural protein VP1 contains the primary binding residues to two EV-A71 receptors, which are, P-selectin glycoprotein ligand-1 (PSGL-1) and scavenger receptor B2 (SCARB2). Additionally, the 3C protein of EV-A71 inhibits the cytosolic receptor retinoid acid-inducible gene I (RIG-I). Subsequently, in infected cells, EV-A71 suppresses the expression of IFN-β, IFN- stimulated gene 54 (ISG54), ISG56 and tumor necrosis factor alpha. This effectively inhibits the initiation of antiviral immunity in the human body [19].

Co-circulation of EV-A71 with other enterovirus A genotype is often seen, and among them the most common type is CV-A16. This leads to recombination events that can give rise to new variants of the virus. Given that RNA viruses lack proofreading and their subsequent increase in susceptibility to mutations it is possible that the current outbreak of 'tomato flu' and its atypical lesions are due to a new variant of CV-A16 [20].

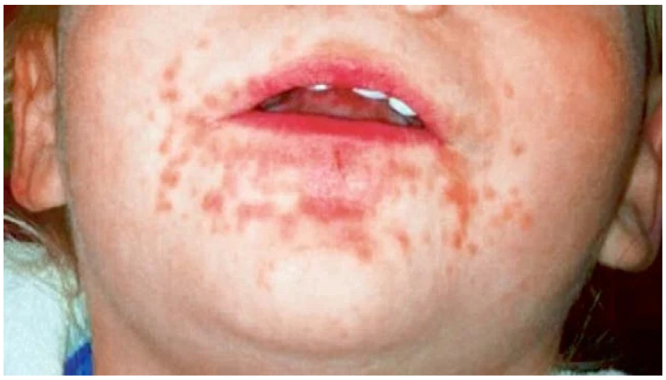

FIG. 4. Macules, papules and vesicles around the mouth of a child due to HFMD (image credit: Daily Mail UK).

Therefore, it is crucial to develop broad-spectrum antivirals to battle the public health burden by these viruses as there is a high possibility of variations of the current HFMD viruses that can expand globally.

2.5. Epidemiology of HFMD

The first case of HFMD was described in Birmingham in 1959. While HFMD is endemic in many countries, outbreaks of EV-A71 associated HFMD has been seen every 2-3 years in Asia-Pacific countries with varying clinical pictures, namely China, Japan, Singapore, Malaysia, Australia, Cambodia, Taiwan, Thailand, South Korea, and Vietnam. Human-to-human transmission of HFMD is possible through fecal-oral route, direct contact, and respiratory droplets [21]. A study done in Guangdong, China suggested that fecal-oral transmission predominated, one possible reason being that the virus could

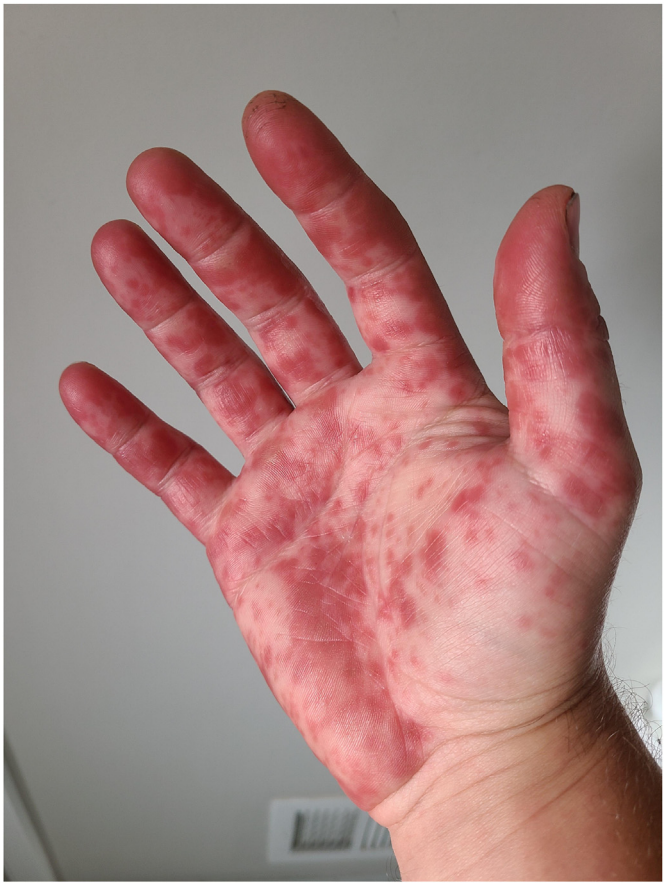

FIG. 5. Maculopapular rash on the palm of HFMD patient (image credit: reddit. com/user/sleekpaprika69).

survive on environmental surfaces. 'Tomato flu' has also been reported to be contagious and transmitted through close contact. Handwashing has been shown to decrease the incidence of HFMD in various studies, supporting these findings.

It is important to note that temperature and humidity may be important factors in the transmissibility of HFMD. A Generalized Additive Model was used to analyze the effect of temperature, humidity, rainfall and windspeed at varying time lags of HFMD in Selangor, Malaysia. They found quantitative evidence that HFMD cases were associated with temperature, humidity, and rainfall at two weeks lag period. Such evidence of transmissibility can be used to help prepare before an outbreak spreads, hence, are important in control and prevention strategies of HFMD.

2.6. Clinical features

Throughout earlier outbreaks of HFMD around the world, different clinical features have been observed in accordance with the virulence of the virus responsible for the outbreak [22]. The primary symptoms observed in the recent outbreak of 'Tomato flu' in India – namely, fever, anorexia (loss of appetite), nausea, vomiting, diarrhea, dehydration, swollen joints and body pain – are similar to that of other viral infections. High grade fever is accompanied by rashes and severe joint pain comparable to those in chikungunya and dengue fever.

One to two days after the onset of fever, small red spots appear on the body which eventually turn into blisters and then to ulcers (Fig. 4). Although they may appear throughout the body, the lesions are usually located on the tongue, inside of the cheeks, gums, palms and soles (Fig. 5). The emergence of rash does not follow either centripetal or centrifugal pattern of dissemination in the body. These blisters are red, painful and may grow to the size of a tomato. It is plausible that the large blisters are due to infection with a new variant of CV-A16. Further research is required to confirm this conjecture [23].

Additional signs and symptoms of 'Tomato flu' include flu-like symptoms such as coughing, sneezing, rhinorrhea (runny nose) and discoloration of the hands, knees and buttocks. Molecular and serological tests are done on children with such signs and symptoms in order to rule out dengue, chikungunya, zika virus, varicella-zoster virus and herpes, following which the diagnosis of 'Tomato flu' can be confirmed. In areas of outbreaks, the disease may be diagnosed clinically by history and physical examination as well [24].

'Tomato flu' caused by the CV-A16 virus is self-limiting and non-life threatening. There have not yet been any deaths reported due to the disease. Complicated and fatal cases of HFMD are predominantly caused by E71 infection. Although infections with CV-A16 are generally thought to be mild, there is potential for development of complications. It primarily affects children and immunocompromised adults. Previously, CV-A16 reportedly caused fatal cases of HFMD in mainland China, France, Japan, Taiwan and the United States. In 2010, 92 cases of HFMD with neurological dysfunction were reported in Shenyang, China [4]. 19 of the reported cases were caused by infection with CV-A16, 2 of which presented with brainstem encephalitis and one with acute flaccid paralysis. Additionally, coinfection with CV-A16 and EV-A71 can cause serious central nervous system complications, leading to severe and prolonged disease states. Therefore, it is plausible that 'Tomato flu' may cause complications and fatalities, especially in immunocompromised children. Follow-up and proper monitoring is required to identify complications and serious outcomes due to tomato flu [25].

2.7. Treatment and prevention

Currently there are no specific antiviral treatments for HFMD. However, multiple prospective antiviral drugs have been explored with some of them showing remarkable results clinically. These include acyclovir and oseltamivir. Patients are advised to rest, stay hydrated and drink clean, filtered water. Ibuprofen or acetaminophen can be used to provide relief from body pain and fever [26].

Proper hygiene and sanitation of the surroundings is necessary to avoid spreading the disease. Furthermore, given the contagious nature of the disease, it is important to isolate confirmed or suspected cases for a period of 5 to 7 days from the day of onset of symptoms to limit transmission of disease. Patients are advised not to scratch the blisters as they may get infected and purulent. The signs and symptoms usually resolve within seven to ten days [27].

2.8. Coxsackievirus A16, "tomato flu" and HFMD

Hand foot and mouth disease is an endemic disease in East and Southeast Asia, mostly affecting children under five years of age. The recent outbreak of HFMD, termed "tomato flu", showed a clinical course similar to those of other viral infections. These include fever, anorexia, rashes, and joint pain. The difference in the clinical picture of this recent outbreak to other outbreaks of HFMD was the appearance of red blisters on skin, and can be due to a new variant of CV-A16 [28].

Tomato flu affected mostly children under the age of 5 years. Coxsackievirus A16, one of the causative agents of HFMD, can easily spread among children in nurseries or primary schools through contaminated fingers, toys or fomites. Another reason for enhanced transmission of HFMD in this age group is that their immune status is relatively low when compared to adults. Since handwashing has been shown to be a protective factor against HFMD it is plausible for children to be affected more as

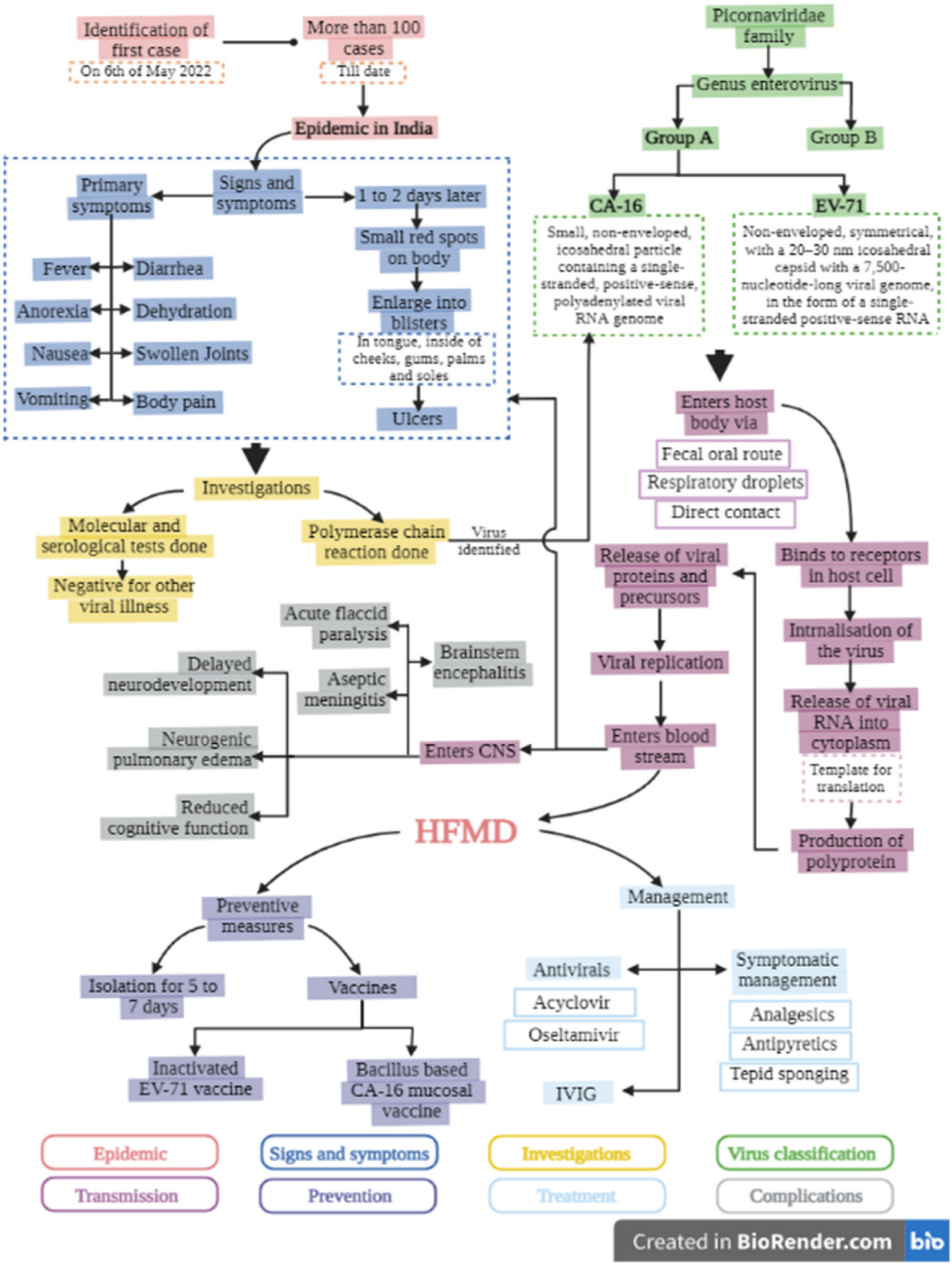

FIG. 6. A summarised diagram on the disease process and management.

they are less likely to wash their hands, and more likely to put their fingers in their mouth than adults [23].

In a retrospective cohort study, adults had been shown to be subclinical carriers or misdiagnosed and hence, they may become the latent infectious source of HFMD. And upon the adults affected with HFMD, most were housewives, students, or teachers. The study also determined risk factors for adult HFMD which included a family size of 4 or more, having a child under 5 years of age, and having a child recently diagnosed with HFMD. These results support the human-to-human transmission of HFMD and why children may be affected more than adults [28].

CV-A16 is a single stranded, polyadenylated RNA virus that belongs to the genus *Picornaviridae* family. It is susceptible to variant formation as the enzyme essential for replication of single stranded RNA lacks proofreading abilities, and this contributes to high mutation rates. CV-A16 has been implicated in the recent outbreak of HFMD in India, and is possibly a new variant. CV-A16 shows tropism to skeletal muscle, lung tissues and brain tissues. High levels of interleukins and interferon-gamma were detected in nasal mucosa, lung and brain tissues. This explains the respiratory infection route of CV-A16, and possibly its CNS pathology [27].

The major causative agents of HFMD are CV-A16 and EV-71. Species of enterovirus-A are responsible for majority of cases of HFMD, such as CV-A16, EV-A71, CV-A6, and CV-A10. Other causes of HFMD include Coxsackievirus-B2, Coxsackievirus-B3, and Coxsackievirus-B5.

Infection with CV-A16 generally causes a self-limiting and non-life-threatening disease (Fig. 6). However, it has propensity to cause fatality, especially in children and immunocompromised adults. CV-A16 has been shown to cause brainstem encephalitis and acute flaccid paralysis in few cases in China in 2010. Furthermore, infection with CV-A16 has caused fatal deaths in various parts of the world. Hence, education to the general public regarding the warning signs of neurologic dysfunction is important in the setting of an outbreak [24].

Acyclovir and Oseltamivir has shown potential benefits in treatment of HFMD. However, HFMD is primarily treated symptomatically, such as with use of Ibuprofen or acetaminophen. There are no licensed vaccines against CV-A16 infection, however, preventive methods such as handwashing has shown to decrease the incidence of HFMD [29].

3. Conclusion

The recent Indian epidemic of 'tomato flu' with large red blisters in the hand, foot and buttocks was later identified to have been caused by a variant of CV-A16. Hence, the term 'tomato flu' is no longer used, and it is identified as yet another outbreak of HFMD. To conclude, timely precautionary measures such as maintaining proper hygiene and sanitation, and five to seven days of isolation following contraction of the disease are important to control the disease and avoid further outbreaks. Although there are no established antivirals for HFMD, acyclovir and oseltamivir have shown effective results by reducing the severity of symptoms. Likewise, the use of immunoglobulins in HFMD has shown to increase clinical cure time and minimize fatality. There are 3 licensed vaccines against HFMD, but only effective against EV-A71. Hence, production of a multivalent vaccine against several etiologies of HFMD, including CV-A16 may be the best preventive method.

Conflict of interest

None declared.

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