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'Tomato Flu' – An outbreak in India with particular emphasis on antiviral therapy

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ABSTRACT:

Recently, some Indian states reported an outbreak of a 'mysterious illness' involving more than a hundred children younger than nine years, with fever and skin lesions. These lesions were more prominent and manifested in the palms, soles, oral cavity, and other body parts. This was initially considered to be a new illness and was described as 'tomato flu'. The disease was contagious but found to be mild in severity. Later in time, it has been identified to be a hand, foot and mouth disease (HFMD), caused by Coxsackievirus-16 (CA-16). So, the term 'tomato flu' should not be used since it is a misnomer for this disease. The mild and uncomplicated HFMD cases usually did not require any antiviral therapy. CA-16 may be associated with a severe, life-threatening HFMD, especially in children with immunocompromised, malnourished, chemotherapy, or underlying medical conditions. However, there are some antiviral agents, intravenous immunoglobulin (IVIG), and vaccines available for the treatment and prevention of HFMD. In this review, we have observed that acyclovir and oseltamivir were effective for patients with serious forms of HFMD. In some cases, the administration of antiviral agents along with IVIG was proven to be more effective. Out of the antiviral agents studied, we observed that oseltamivir and acyclovir were effective with less adverse effects. Three inactivated whole-virus EV-71 vaccines have been licensed, while a recombinant VP1 vaccine against CA-16 is under development. Many types of research revealed that there are many potential and prospective antiviral candidates that can be employed in the near future. The antiviral drug umifenovir (arbidol) was found to be very effective against HFMD under in vivo *laboratory conditions. There were some prospective antiviral agents, required to pass through phases of clinical trials.*

Keywords: Tomato flu, Hand, foot and mouth disease, Coxsackievirus A16, Antiviral drug, Vaccine, Intravenous immunoglobulin.

INTRODUCTION

After a dramatic and devastating disruption caused by the COVID-19 pandemic for nearly 2 years now, as the world is slowly returning to normality with the slowed down spread of SARS-CoV-2, other viral and bacterial outbreaks have started to take over[1]. Recently, on May 6, 2022, a viral infection named 'tomato flu' emerged in India in the state of Kerala[2]. This rare viral infection got its name from the vegetable 'tomato' due to the bright red blisters that spread all over the body of the affected children, which gradually grew to the size of a tomato[3]. These blisters are accompanied by symptoms very similar to other viral illnesses, such as fever, fatigue, and body aches[4]. This illness is considered to be very contagious and till date from its outbreak the disease has been detected in more than 100 children in India under the age of 9[5]. Although the disease is not life threatening, with no death records, it has to be noteworthy that the disease can be very painful[6].

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Earlier, there were speculations about this disease being an after effect of chikungunya or dengue infection caused by the vector mosquitoes[3]. Upon getting negative results for the serologies done to detect these conditions, polymerase chain reaction was performed for enteroviruses (EV) and monkeypox[7] at a national reference laboratory in the United Kingdom (Porton Down, Salisbury). Further sequencing at another national reference laboratory (UKHSA-Colindale) led to the identification of Coxsackie A16 (CA-16) serotype as the main causative agent of the disease[7]. CA-16 is a common cause of hand, foot and mouth disease (HFMD), a contagious viral disease which usually affects infants and children younger than 5 years.[8] Hence, the term 'tomato flu' is now considered a misnomer that should no longer be used, as HFMD is a well-known disease[9].

HFMD can be caused by more than 20 enteroviruses, with CA-16 and enterovirus A71 (EV-A71) being the most common ones[8]. These viruses belong to the Picornaviridae family[10]. CA-16 is a very small, non-enveloped, icosahedral particle containing single stranded, positive sense, viral ribonucleic acid (RNA) genome[11]. EV-A71 particle is non-enveloped, symmetrical, with a 20-30 nm icosahedral capsid with a 7,500 nucleotide long viral genome, in the form of a single-stranded positive-sense RNA[12]. The spread of these enteroviruses is mediated by contact with an infected person's saliva, faecal matter, respiratory aerosol droplets, or contaminated water[13,14]. After ingestion, the virus spreads to the regional lymph nodes through replication in the lymphoid tissues of the lower intestine and the pharynx[13]. Children under 5 are the most susceptible to the disease due to a weaker and partially developed immune system[14]. Immunocompromised adults may also contract HFMD[2]. The affected individuals are more prone to transmit the disease during the first week of infection[14]. The infection usually involves hands, feet, and mouth, although at times involvement of genitals and buttocks are observed[8]. Severe and fatal cases of HFMD have been encountered with EV-A71 strain, and CA-16 is generally thought to cause only mild symptoms such as blisters or ulcers over the body[11], although, in a minority of cases, CA-16 patients have also developed aseptic meningitis, encephalitis, and even fatal myocarditis and pneumonia[11].

In CA-16, 3C proteases are identified to be important in the process of viral replication where its function is to activate the mitochondrial pathway related caspase 9 protein and the Fas death receptor pathway related caspase 8 protein[14]. Following activation of these pathways, host cell deoxyribonucleic acid (DNA) fragmentation occurs, leading to its death[14]. Viral replication is assisted by the 2 non-structural proteins, 2C and 3C, which prevents viral RNA degradation by hindering the fusion of autophagosomes with lysosomes[14].

Global epidemiology of HFMD had been well documented in the past decade, during large scale outbreaks in Japan, Singapore, and China, which resulted in substantial costs of epidemics to the economy and public health concerns worldwide[15]. Timely preventive measures can greatly reduce the magnitude and distribution of infection[15]. There are no pharmacological treatments for HFMD[15]; however, acyclovir was used with a good treatment outcome[17].

In this article we are discussing the recent HFMD outbreak in India with particular emphasis on antiviral drug therapy.

TREATMENT STRATEGY

Due to the recent emergence of 'tomato flu', there are no specific antiviral drugs or vaccines for the disease yet[2]. Parents are advised to seek medical attention if their children show signs and symptoms of 'tomato flu'[18]. However, due to the self-limiting nature of the disease, it is primarily managed symptomatically. The management guidelines are similar to that of chikungunya, dengue and typical HFMD. Patients are advised to rest, stay hydrated and to drink clean, filtered water[2,18,19]. Ibuprofen or Acetaminophen can be opted to treat fever and bodyache[2]. Aspirin should not be given to children[19]. Steroids should be avoided as it has been linked with an increased risk of severe HFMD development[20]. Patients are advised not to scratch or rupture the blisters[21]. Antibiotics are not required unless the blisters are infected and become purulent[21]. The signs and symptoms typically subside within seven to ten days[2]. Proper hygiene and sanitation should be maintained throughout the course of the disease[2,21].

Parents of children with HFMD are advised to seek urgent medical attention if the child is refusing to drink enough fluids to stay hydrated[20]. They should be educated about the signs of dehydration such as dry mouth, lips, and eyes, and reduced urine output with dark and strong-smelling urine. Additionally, medical attention is required if the symptoms do not improve after 10 days, or if the symptoms are very severe. Immunocompromised children and very young children should also be seen by a healthcare provider[20], especially if they are younger than 6 months. Education regarding the warning signs of neurologic dysfunction, such as increased drowsiness and seizures, is important in order to avoid dire consequences.

PREVENTION OF THE DISEASE

Prevention is important to control the disease and avoid further outbreaks. Close contact with infected individuals should be avoided. Affected children are advised to be isolated for five to seven days[2,20]. Clothes, utensils and toys used by the patients should be washed and disinfected. Parents of affected children should also follow good hygiene and sanitation practices. They are advised to wash their hands with soap and water or to use an alcohol-based hand sanitizer for at least 20 seconds before and after caring for the sick child[20]. Along with proper sanitation and hygiene, following a well-balanced diet in order to maintain good immunity is important.

ANTIVIRAL THERAPY

Currently, there are no specific antiviral treatments for hand, foot and mouth disease[20] and hence, none are used in the treatment for 'tomato flu'. There are drug candidates for the treatment of HFMD. Several antiviral drugs are used as adjuvant therapy in combination with other medications. The following paragraphs will explore the scope of antivirals in HFMD. However, in the past, literature has mainly focused on EV-71 as it is predominantly linked with severe and fatal cases of HFMD. Nevertheless, successful development of medications and vaccines against EV-71 will provide insight and inspiration for the production of remedies against CA-16.

Acyclovir

Despite the usual mild disease course of HFMD, it can cause severe disease and complications that are life threatening, and sometimes even cause death. Oral acyclovir has shown potent action against severe cases of HFMD within the past years. Lesions in HFMD can be infectious until full resolution[22]. Acyclovir has exceptional symptomatic relief especially on these characteristic lesions[22]. Subsequently, it contributes to the cessation of spread of the disease in addition to the prompt ease of the symptoms[22].

A case report by Damle[22] demonstrated the therapeutic effect of acyclovir administration where 3 severely ill children aged 1-2 years, with atypical lesions, high fever and high irritability, who were refusing to eat, showed remarkable results after administration of the drug. A similar significant result was demonstrated in 1996 by Shelley et al[23]: 12 children aged 1-5 years and one adult obtained defervescence, marked involution of lesions and symptomatic relief within 24 hours from acyclovir administration. These patients were given oral acyclovir 200-300 mg five times a day for 5 days within 1-2 days of onset of rash[23].

Acyclovir inhibits viral DNA by the action of acyclovir triphosphate[24]. Acyclovir is converted to acyclovir triphosphate by the action of thymidine kinase, which is released from infected cells[24]. This inhibits viral DNA replication *via* strong binding to the viral DNA polymerase[24]. However, since enteroviruses are still RNA viruses, they lack thymidine kinase[24]. Therefore, it is thought[24] to cause its therapeutic antiviral effect on HFMD cases by indirectly augmenting patients' own interferons.

Hypersensitivity is the only known absolute contraindication for acyclovir[25]. Attention should be given when administering acyclovir for patients with renal failure or impairment, immunocompromised, possible risk of thrombotic thrombocytic purpura (TTP) and haemolytic uremic syndrome (HUS)[25].

The side effects of acyclovir vary with the route of administration. Topical application of this drug may cause stinging and burning sensation after each application[26]. Oral administration is well tolerated; however, there are reported cases of headache, nausea, malaise, and some effects on central nervous system (CNS)[26]. Intravenous administration may lead to rashes, sweating, vomiting and a decrease in blood pressure has been noted[26] in a few patients.

The most important toxicity to consider is the dose dependent decrease in glomerular filtration rate, that is commonly seen in patients with kidney disease[26]. This effect returns to normal on discontinuation[26]. With higher doses, reversible neurological symptoms, such as tremors, hallucinations, disorientation, lethargy, convulsions, and coma, are recorded. There is no known teratogenic effect of acyclovir[26].

Oseltamivir

Oseltamivir is a neuraminidase inhibitor used in the prophylaxis and treatment of influenza[27]. At present, this drug is increasingly used as an adjunctive therapy in combination with other medications for the treatment of HFMD in China[27]. Several studies[27] have been done to show its effect on HFMD and has resulted in positive outcomes.

A meta-analysis[27] of randomized clinical trials was done on eligible studies from inception to October 10, 2020, by inquiring six databases (PubMed, Embase, CENTRAL, CNKI, Wanfang and VIP databases). 91 studies were retrieved from the initial study; however, in the final analysis, 11 studies were included, involving 977 HFMD children. The meta-analysis confirmed that oseltamivir showed effectiveness against the disease, with shorter fever clearance time, shorter rash regression time, and shorter clinical cure time. The study[27] showed no further increased risk of adverse reactions for the treatment of HFMD in children.

EV-71 is a major causative agent of HFMD that could result in death of children and affects the central nervous system[27]. In the human body, EV-71 responds to sialic-acid-linked glycan, which is abundantly expressed in the respiratory and gastrointestinal tracts, and dendritic cell-specific intercellular adhesion-molecule-3-grabbing non-integrin[27]. This has been identified to be a receptor where EV-71 binds and attaches to the host cells[27]. This sialic acid link is thought to be a common pathway by which oseltamivir exerts its therapeutic effect against the enteroviruses in HFMD[28]. Oseltamivir, which is an oral prodrug, gets hydrolyzed by the hepatic esterase into active oseltamivir carboxylate upon ingesting[28] (Figure 1). A lipophilic side chain of this active drug inhibits the ability to cleave sialic acid residues on the surface of the infected host cells by binding to the virus' enzyme[27,28]. Oseltamivir is also recognized to be a treatment for acute encephalitis caused by HFMD by reaching through the blood brain barrier[27].

Oseltamivir is generally well tolerated, although some side effects such as nausea, vomiting, abdominal pain, diarrhea, headache, insomnia, and vertigo can be seen[29]. Almost 16% of children aged 1-12 years report vomiting as the most frequently encountered side effect[29]. In addition to these, rarely conjunctivitis, epistaxis, allergy, arrhythmia, gastrointestinal bleeding, ery-

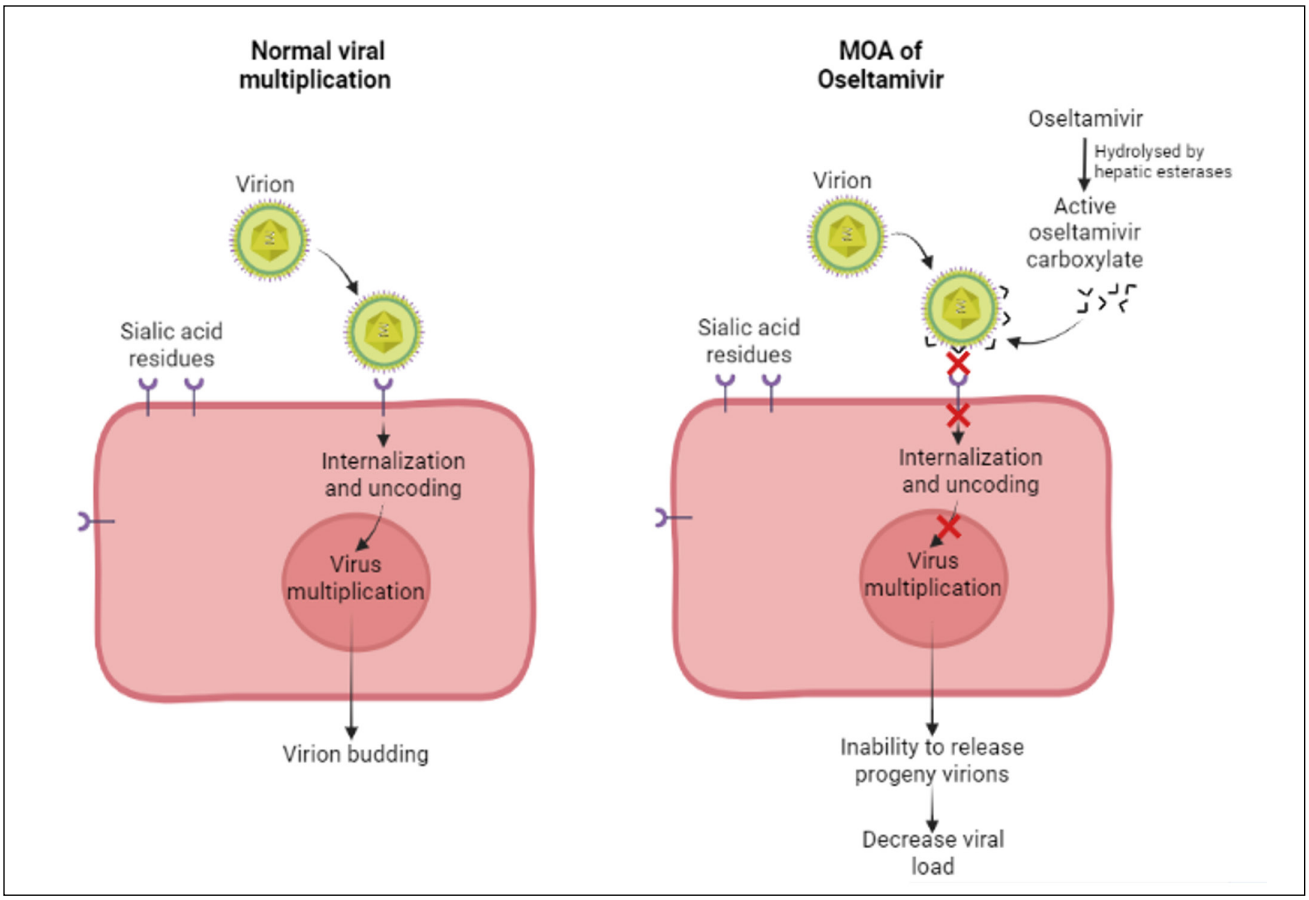

Figure 1. Mode of action of Oseltamivir (created in BioRender.com).

thema multiforme, Stevens Johnsons syndrome (SJS), toxic epidermal necrolysis (TEN), confusion, hepatitis, seizures, and neuropsychiatric events can occur[29].

Despite the efficiency of this drug in treating HFMD in children, the risks of taking the medicine must be considered. The drug must be avoided in cases of allergies to oseltamivir or a component of the formulation and in patients with hereditary fructose intolerance[29]. One must also look out for gasping syndrome in neonates as the suspension consists of sodium benzoate[29].

Arbidol (Umifenovir)

A study on the antiviral agent Arbidol (ARB), ethyl-6-bromo-4-[(dimethylamino)-methyl]-5-hydroxy-1-methyl-2-[(phenylthio)methyl]-indole-3-carboxylate hydrochloride monohydrate was done against a range of human respiratory viruses that included the enterovirus Coxsackie virus B3 (CB-3) *in vitro* in cell culture[30]. This study demonstrated that ARB showed potent inhibitory activity when it was added before, during or after viral infection with 50% inhibitory concentration (IC50) ranging from 2.7 to 13.8 µg/ml, against enveloped and non-enveloped RNA viruses[30].

The virus known to cause HFMD, CA-16, is a non-enveloped virus with linear single stranded RNA, therefore the effect of ARB on the viruses assessed in this study can be applicable to CA-16[30]. ARB is currently more commonly used as an antiviral against influenza. It is approved for use in Russia, China, and some other countries[31]. The primary mode of action of ARB is the inhibition of virus entry and/or the fusion of viral membranes with intracellular endosomal membranes. A study by Herod et al[32] demonstrated that ARB inhibits replication of the virus causing HFMD, although further studies are required to identify the exact mechanism of how the replication is inhibited. Children under 2 years are known to have increased sensitivity to the medication[33]. Possible allergic reaction of a rash is rare[33]; however, some adverse reactions can include nausea, diarrhea, dizziness and elevated serum aminotransferase (AST)[34].

Chloroquine Diphosphate (CQ)

A study by Tan et al[35] tested chloroquine against serotypes associated with HFMD. The strains used were EV-A71, CA-6 CA-16 and E-7. The test used rhabdomyosarcoma cells (RD cells) to assess the efficacy of chloroquine diphosphate (CQ) in inhibiting the HFMD viruses and the therapeutic capacity was tested in murine model (Balb/c pups) of EV-A71 infection[35]. In this study[35], first the effect of CQ treatment on replication of EV-A71 was evaluated *in vitro* by the viral protein synthesis and by production of the infectious virus. Subsequently, depending on the production of EV-A71, it was

then used for the *in vivo* study that was performed in a murine model to assess the potency of CQ as an antiviral agent against this virus.

The results revealed that RD cells inoculated with CQ showed dose dependent antiviral activity against the tested serotypes in pre-treatment (treatment 2 hours before virus inoculation), post treatment (treatment after 2 hours and every 24 hours for 6 days) and in combination treatment (treatment before 2 hours and every 24 hours for 6 days)[35]. This established antiviral activity of CQ against EV in cell-based investigations[35]. CQ was found to be effective in protecting immunocompetent neonatal mice against a lethal dose of EV-A71, which increased the survival rate of the mice and decreased the severity of clinical symptoms as well[35]. Therefore, considering both of the above, CQ can be considered as a potent and efficient broad acting antiviral against viruses causing HFMD[35]. In another study by Dias et al[36], chloroquine was found to inhibit viral replication by hindering the pH dependent steps of the coxsackie viruses.

Rupintrivir

Rupintrivir was developed initially against rhinovirus 3C protease[37]. An *in vivo* study[37] performed to assess the antiviral activity of rupintrivir against EV-A71 tested on suckling mice showed that it effectively protected them from severe disease, at a dose of 0.1 mg/kg. It prevented limb paralysis and markedly improved its survival[37]. Further histological, immunohistochemical and quantitative RT_PCR analysis confirmed that it also remarkably reduced virus-induced necrotizing myositis, suppressed viral RNA and blocked the expression of EV-A71 in various tissues, making it a strong inhibitor of spread of the virus and severe illness[37].

In addition, a molecular dynamic study[38] using all-atoms-molecular dynamics simulation was done to assess potential inhibition of rupintrivir, and a peptide α, β-unsaturated ethyl ester (SG85) against 3C protease of coxsackievirus A16 and enterovirus A71 in 2016. The EV has a polyprotein precursor virus that gets cleaved into four structural sub parts (vp1, vp2, vp3, and vp4) and seven NS proteins (2A, 2B, 2C, 3A, 3B, 3C and 3D)[39,40]. This is achieved thanks to the action of the enzymes 2A and 3C proteases[39,40]. While the 2A protease (2Apro) cleaves the joint between VP1 and 2Apro, the rest of the 8 junctions are cleaved by 3C protease (3Cpro)[39,40]. The peptide bond cleaved by 3Cpro cysteine protease during the viral replication process is between glutamine and glycine of the viral protein[41]. This effectively inhibits the viral replication process[41]. This establishes rupintrivir as one of the main drug targets for CA-16.

Antiviral Aptamers for Inhibition of HFMD Associated Viruses

Aptamers are small, artificial, single-stranded DNA- or RNA-based nucleotides in the range of 10-100 nucleotides that can bind to their targets with high specificity and sensitivity[42]. Aptamer-based therapeutic drugs work in the same way as monoclonal antibody[42]. They are promising in antiviral therapy[43] and can potentially be used as an antiviral agent against etiologies of HFMD. DNA aptamers, V11 and V21, with high specificity and affinity for VP1 protein of EV-71 were screened by systematic evolution of ligands by exponential enrichment (SELEX) technology[44]. These aptamers were found to have apparent effect of inhibiting EV-71 infection *in vitro*, proving that they had potential value in the treatment of EV-71[44].

Treatment Using Intravenous Immunoglobulins (IVIG)

The use of intravenous immunoglobulins (IVIG) has been suggested for the treatment of HFMD based on evidence[20] of a possible significant benefit through reduction of the associated CNS inflammatory response. It has also been indicated, through anecdotal experiences in Asia, that IVIG, if administered early, could halt disease progression to autonomic nervous system involvement and subsequently to often fatal pulmonary edema[45]. However, the use of IVIG as a treatment modality for HFMD is contentious. This is in concordance with the fact that HFMD is caused by a large number of enterovirus types and subtypes, IVIGs may not contain adequate quantities of antibodies that are able to neutralize the infecting agent[20]. Moreover, *in vitro* studies[46] have found that, while IgG1 and 2 subclasses of human IVIG have neutralizing activity, IgG3 fraction of human IVIG does not, and instead enhances EV-A71 infection.

There are studies[47,48] done on the efficacy and dosage of IVIG in patients with HFMD. In a retrospective study[47] done in Shanghai, China, IVIG was used in the treatment and management for children with HFMD with neurologic complications. Because of the high price of IVIG and the safety concern of it being a human blood product, all the children with HFMD did not receive IVIG as a treatment method[47]. The children that received IVIG had a shorter duration of fever, vomiting, startle, myoclonic twitching, and length of stay than those who did not receive IVIG[47]. They were recovered and discharged without any complications[47], which shows the efficacy of IVIG in the treatment of severe HFMD. A meta-analysis[48] performed in Children's Hospital of Chongqing Medical University found that IVIG improves HFMD, with a high dose giving better prognosis. The study showed that the IVIG group had a higher total effective rate, shorter fever relieving time, rash regression time, remission time of neurological symptoms, mouth ulcer regression time and average length of stay compared to conventional therapy alone[48]. For patients with severe HFMD, high dose IVIG can be used based on the good potency ratio and safe treatment result, while low dose IVIG can be used in stable patients to reduce costs[48].

There are a number of adverse effects with the use of IVIG which can be local (at the infusion site) or sys-

temic, involving the body as a whole or a specific organ or system[45]. Local adverse reactions arise at the needle site which causes pain, bleeding or bruising[45]. It may also occur when venous access is difficult or if there is fluid extravasation into the tissues causing prolonged pain and swelling[45]. Systemic adverse reactions are common, and the most immediate reactions are chills, fever, headache and muscular pain. These symptoms are mild and occur within an hour from starting an infusion and disappear within 6 hours[45]. Moderate adverse effects include persistent headache, aseptic meningitis, hemolytic anaemia, serum sickness and dermatologic complications[45]. Severe adverse effects of IVIG include anaphylactic reactions, renal complications, pulmonary complications, thrombosis and embolism, colitis and blood borne infectious diseases[45]. A large infusion volume is required in administration of IVIG and often these children are already experiencing hypertension and tachycardia[45].

The dosage of IVIG differs depending on the clinical scenario. The advised total dosage of IVIG for most indications is 2 g/kg body weight[45]. IVIG is given in 2 doses for HFMD, each dose being 1 g/kg body weight[45]. The first dose is given over 8-12 hours, while the second dose is given 24 hours after the first dose, as advised by the treating physician[45]. A higher regimen of 3 or 4 doses of 1 g/kg has been prescribed by doctors, whereas a lower dose of 0.5 or 1 g/kg has been given according to the clinical situation which has been found efficacious[45].

Immunoprophylaxis with Vaccines

An enterovirus 71 (EV-71) vaccine was introduced in Chengdu, China, in 2016 as a paediatric immunization program[49]. This vaccine was developed as a monovalent, inactivated whole-virus vaccine against EV-71 by the Institute of Medical Biology, Chinese Academy of Medical Sciences (CAMS) and was licensed in December, 2015[50,51]. In January 2016, a Vero cell-based vaccine with aluminium hydroxide was developed by Sinovac Biotech Co.[52], and in 2016 an inactivated alum-adjuvanted EV-71 vaccine by Vigoo Biological Co. was also licensed[53]. The vaccines administered in Chengdu were produced by CAMS and Sinovac[49]. Randomized, double-blind, placebo-controlled phase 3 trials among healthy children aged 6-35 months, demonstrated a vaccine efficacy against EV-71-associated HFMD of over 98% after two doses[51,52].

A longitudinal surveillance study[49] was done in Chengdu to study the impact of the inactivated EV-71 vaccine against HFMD after it was introduced in 2016. Reported HFMD cases between January 1, 2011, and December 31, 2018, were obtained from China's National Infectious Disease Reporting System[49]. The study reported a lower-than-expected incidence of EV-71-specific HFMD cases, along with a decline in severe HFMD cases in the years following the vaccine introduction (2017-2018), while the proportion of CA-16 cases remained stable[49]. However, more cases than predicted of HFMD caused by non-CA-16 and non-EV-71 enteroviruses in 2018 were reported in the same study[49]. These changes suggest that the decline in cases of EV-71-specific HFMD were likely due to the vaccine rather than environmental factors[49]. The increase in HFMD cases caused by other serotypes may have resulted from vaccine-driven serotype replacement[49].

Co-infection of CA-16 with EV-71 is possible and might increase the possibility of genetic recombination between CA-16 and EV-71[54]. Hence, this inactivated vaccine against EV-71 is a possible preventive measure that could be applied in Kerala, India, during this recent outbreak of HFMD or 'tomato flu'. However, as the EV-71 vaccine does not confer protection against other etiological agents of HFMD[49], the need for exploration of other vaccines persists. Another potential vaccine against HFMD is a *Bacillus*-based CA-16 mucosal vaccine that can stimulate production of neutralizing antibodies *via* intranasal immunisation[55]. This is the first vaccine that was introduced for the prevention of CA-16 infection[55].

VP1 gene of CA-16 was amplified and inserted into the CotB gene of *Bacillus subtilis via* recombination and expressed on the surface of *Bacillus* spores[55]. This vaccine was used for intranasal immunization of mice, inducing a significantly higher level of VP1 specific IgA and IgG compared to the non-immunized group[55]. A specific neutralizing antibody titer in the immunized group was also significantly higher than that in the control group[55]. These results suggest that the mucosal vaccine can increase the titer of the specific antibody as well as the titer of the neutralizing antibody. This study provides a foundation for the possible development of a vaccine against CA-16[55], that could potentially be used as a preventive measure for CA-16-specific HFMD.

'Tomato flu' (HFMD) is a self-limiting disease and is primarily managed symptomatically. There are no specific antivirals advised for the treatment of HFMD as of yet[2]. Supportive therapy is the primary treatment which includes ibuprofen or acetaminophen for fever and bodyache[2]. Parents are advised to avoid scratch or rupture of the blisters and to maintain proper hygiene and sanitation[2,21]. Moreover, antibiotics are used only if the blisters become infected and purulent[21]. Steroids are linked with increased risk of severe HFMD and hence, should be avoided[20].

There have been no reports of severe disease in 'tomato flu' (HFMD) to this date[2,6]. However, in the past, there have been cases of severe HFMD reported with the virus CA-16[11,56,57]. Although EV-71-positive cases has been found to have a higher mortality rate than CA-16-positive cases[56], severe and fatal CA-16-positive cases have also been reported[11]. Serious complications, such as aseptic meningitis, encephalitis and fatal myocarditis and pneumonia have been reported in a small number of patients[58-60]. Moreover, some patients having been co-infected with EV-71 and CA-16, experiencing CNS complications[11] and increasing chances of genetic recombination of EV-71 with CA-16[54].

There are no antivirals approved for the treatment of HFMD[20]. However, there are established antivirals that have been proven to be effective against severe cases of HFMD[22,24]. Five antivirals has been discussed in this article; oseltamivir, chloroquine diphosphate, acyclovir, rupintrivir and arbidol (umifenovir). Out of these, acyclovir and oseltamivir have been established as effective in severe cases of HFMD[22,24].

Oral acyclovir has shown the highest power against severe cases of HFMD[22]. When the cells are infected with the virus, they release thymidine kinase, which converts acyclovir into its active metabolite, acyclovir triphosphate[24]. This active metabolite strongly binds to the viral DNA polymerase and results in inhibition of viral DNA replication[24]. However, enteroviruses lack thymidine kinase because they are RNA viruses, hence it is thought that acyclovir exhibits its therapeutic effect on cases with HFMD by indirectly augmenting the patient's own interferons[24]. The side effects of acyclovir vary with the route of administration, and it may also cause complications, such as TTP and HUS in those who are immunocompromised or have renal failure[25]. Topical application of acyclovir may cause stinging and burning sensation after each application. Oral administration, however well tolerated, has been reported to cause headache, nausea, malaise and some CNS effects. Intravenous administration may lead to rashes, sweating, vomiting and a decrease in blood pressure[26].

Oseltamivir has been confirmed to show effectiveness against HFMD in randomized clinical trials[27]. It is increasingly used as an adjunctive therapy for the treatment of HFMD in China[27]. Oseltamivir upon ingestion, gets hydrolyzed by hepatic enterases into active oseltamivir carboxylate[28]. A lipophilic side chain of this active drug binds to the virus' enzyme and inhibits the ability to cleave sialic acid residues on the surface of the infected host cells[27]. Some of the side effects that can be seen are nausea, vomiting, abdominal pain, diarrhea, headache, insomnia and vertigo[29]. Rarely, conjunctivitis, epistaxis, allergy, arrhythmia, gastrointestinal bleeding, erythema multiforme, SJS, TEN, confusion, hepatitis, seizures and neuropsychiatric events can also occur as a result of oseltamivir[29].

Arbidol, CQ, and rupintrivir have been described as prospective antivirals in the article. Arbidol is currently used as an antiviral agent against influenza[31;] however, *in vitro* studies[30] done showed potent inhibitory activity against enveloped and non-enveloped RNA which could be applicable to CA-16, a non-enveloped RNA virus. Research[32] done on arbidol has demonstrated that it inhibits viral replication in cases with HFMD. Nevertheless, further studies are required to identify the exact mechanism. The related side effects of arbidol include nausea, diarrhea, dizziness and elevated serum AST.

CQ was tested against EV-A71, CA-6, CA-16 and E-7 in rhabdomyosarcoma cells to assess the efficacy[35]. This study established the dose dependent antiviral activity against the enteroviruses[35]. An additional study[36] further explains that CQ inhibits viral replication by hindering the pH dependent steps of the coxsackie viruses. Another such prospective drug, rupintrivir, has been found to have potential inhibition against 3C protease of CA-16[38]. The 3C protease is cysteine protease, involved in the viral replication process; therefore, inhibition of this enzyme by rupintrivir will lead to inhibition of this process[38]. Further studies are needed to determine the exact mechanism of action of these drugs and the efficacy and potency against HFMD.

There is debate surrounding the use of IVIG as a treatment modality for HFMD[20,46]. However, studies[47,48] have shown that there was a shorter duration of symptoms and length of stay among those who received IVIG. Moreover, IVIG in higher doses is an effective treatment modality in those with severe HFMD based on good potency ratio and safe treatment results[48].

There are 3 licensed vaccines against HFMD, but they act on the virus EV-71 only[50-53]. The use of these vaccines has shown a decrease in prevalence of EV-71-positive and severe HFMD cases, but more cases of non-CA-16 and non-EV-71 enteroviruses have been reported[49]. Hence, the need for a multivalent vaccine against HFMD has increased. Vaccines that work against CA-16, the virus confirmed to cause 'tomato flu[7]', are not available[55]. However, a *Bacillus*-based CA-16 mucosal vaccine has been introduced, thus it can stimulate production of neutralizing antibodies *via* intranasal immunization[55]. This study[55] done on mice has shown in its results that mucosal vaccine can increase the titer of the specific antibody, as well as the titer of the neutralizing antibody. There is prospect of introduction of vaccines against HFMD serotypes other than EV-71 which can be accomplished by further studies and research. The overall therapeutic strategy involved in treating HFMD cases is given in Figure 2.

CONCLUSIONS

The recent outbreak of HFMD in India was initially thought to be of a new virus and wrongly termed as 'tomato flu' due to the presence of red blisters on skin. While the disease is not life-threatening, it may progress to cause neurologic dysfunction such as encephalitis as in previous outbreaks of HFMD, especially in immunocompromised people. Although the use of antivirals for HFMD is not established, acyclovir and oseltamivir have shown effective results in the treatment of HFMD by reducing the clinical cure time. Supportive therapy helps reducing the symptoms of HFMD and is the current initial mode of treatment. Coxsackievirus A16 has been implicated in the recent outbreak in India and is a predominant cause of HFMD worldwide along with Enterovirus 71. These viruses are the targets for vaccine prevention strategies of HFMD. The use of immunoglobulins in HFMD has shown to decrease its symptoms' duration and minimize progression to complications.

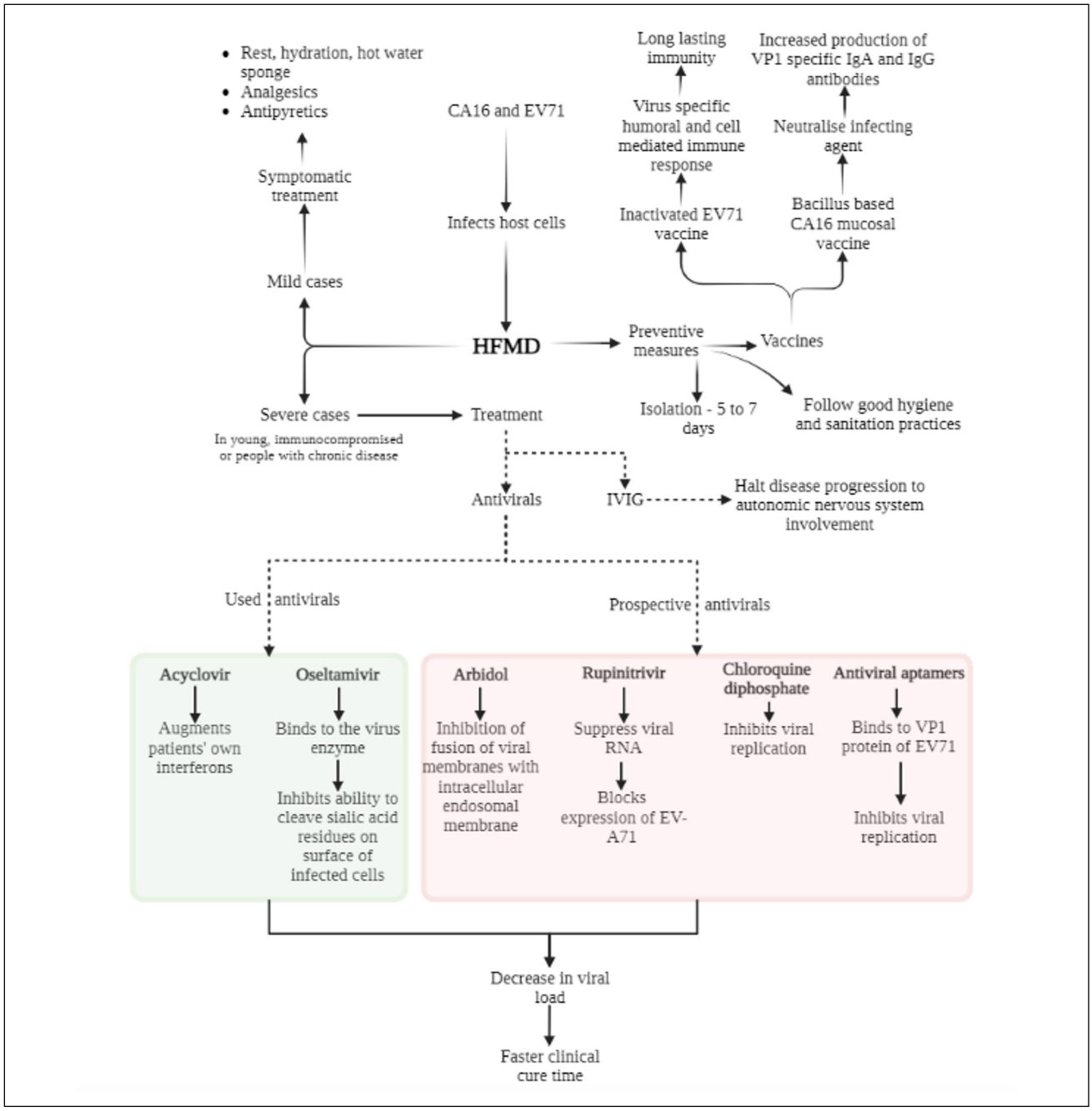

Figure 2. Therapeutic strategy for hand, foot and mouth disease (created in BioRender.com).

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