

Three Cases of Intra-familial Transmission of Hand, Foot and Mouth Disease Treated with Acyclovir

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Abstract Background: Hand, foot and mouth disease (HFMD) is a viral illness that presents mainly in children but also in adults with constitutional symptoms such as low-grade fever, malaise, and myalgia in addition to macular, maculopapular, or papulovesicular skin lesions on hands, feet, and mouth. No specific antiviral therapy is available for HFMD as most cases have a benign clinical course with complete resolution of symptoms and signs within 7 to 10 day. To our knowledge, three previous studies have demonstrated prompt symptomatic relief and shortened disease course after initiating treatment with acyclovir. **Case Presentation:** Three cases of intra-familial transmission HFMD including two young siblings (2-year-old boy and 4-year-old boy) and their 37-year-old immunocompetent mother. The diagnosis was made clinically and therapy with oral acyclovir was initiated within 24 hours of first lesion appearance for all three cases. The young siblings received oral acyclovir 200 mg four times daily, while their immunocompetent mother received acyclovir 800 mg four times daily. In the two young siblings, new lesions stopped appearing and most existing lesions showed noticeable involution after a single day of treatment. Significant reduction in pruritus and defervescence were also noted at this time. Complete resolution was achieved with three days of acyclovir therapy. The single vesicle observed on their mother showed complete resolution after a single day of treatment. **Conclusion:** We present three studies of HFMD successfully treated with acyclovir to demonstrate the therapeutic benefit of acyclovir for symptomatic HFMD in young children and adults. Early initiation of oral acyclovir may influence the disease course by shortening the duration and intensity of symptoms. In the case of outbreaks, in particular, acyclovir should be considered as it may offer benefit to the population at large. We recommend a randomized, controlled trial to further investigate the therapeutic role of acyclovir in HFMD.

Keywords: hand, foot and mouth disease, acyclovir, pediatric rashes, coxsackievirus

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1. Introduction

Hand, foot and mouth disease (HFMD) is a highly contagious viral illness caused by enteroviruses of the Picornaviridae family. Children younger than ten years are most commonly affected with outbreaks occurring in daycare centers and summer camps, particularly in late summer and early autumn months. However, all age groups including adults may be affected [1,2]. Typical clinical symptoms include low-grade fever, malaise and myalgia followed by a rash that has been described as macular, maculopapular, or papulovesicular. The rash is most commonly seen on the extremities and buttocks, and less commonly the torso and face.

Over 15 enterovirus serotypes have been shown to cause HFMD, most commonly coxsackievirus A serotypes. Coxsackievirus A16 (CVA16) and enterovirus A71 (EV71) are responsible for the majority of large outbreaks [4]. HFMD caused by CVA16 is usually self-limiting without

complications, whereas EV71-induced HFMD may cause severe illness complicated by central nervous system disease, pulmonary hemorrhage and heart failure [5]. In the recent years, coxsackievirus A6 (CVA6) and coxsackievirus A10 (CVA10) have been widely associated with both sporadic cases and outbreaks of HFMD worldwide, particularly with an increased frequency of neurological complications and mortality [6]. No specific antiviral therapy is available for HFMD as most cases have a benign clinical course with complete resolution of symptoms and signs within 7 to 10 days [9]. Rarely, HFMD is complicated by myocarditis, pneumonia, meningitis, encephalitis and pancreatitis [3].

2. Case Presentation

Case 1: 2-year-old male

A 2-year-old male accompanied by his mother presented to the primary care clinic in late summer with a 1-day history of low grade fever and malaise followed by

multiple papulovesicular eruptions and evolving blisters on his legs, buttocks and genitals, shown in [Figure 1](#) and [Figure 2](#). Development of lesions were noted on both palms and feet on the same day, shown in [Figure 3](#) and [Figure 4](#). Further examination revealed few small vesicles on the buccal mucosa with some superficial ulcerations. However, oral lesions were not painful. Patient's mother reported a case of HFMD at her son's daycare one week before his illness began.



Figure 1. Extensor surface of knee of 2-year-old male showing vesicles and blisters



Figure 2. Posterior leg of 2-year-old male showing vesicles and blisters



Figure 3. Palms of 2-year-old male showing scattered papules



Figure 4. Foot of 2-year-old male showing papulovesicular eruptions

Case 2: 4-year-old male

A 4-year-old male accompanied by his mother presented to the primary care clinic with a 1-day history of low grade fever and malaise followed by a single pruritic vesicle on his hand 24 hours after his brother received the diagnosis of HFMD. Oral cavity was spared.

Case 3: 37-year-old female

A 37-year-old female presented with a single pruritic vesicle on her hand preceded by low-grade fever and malaise. Vesicle appeared 24 hours after her 4-year-old son was diagnosed with HFMD. Patient's medical history was significant for follicular lymphoma, a subtype of non-Hodgkin lymphoma, diagnosed 10 years ago. Patient underwent successful surgical excision with subsequent radiotherapy for localized disease without recurrence. Complete blood count one month ago revealed no abnormalities, and she was considered immunocompetent at this time.

The diagnosis was made clinically and therapy with oral acyclovir was initiated within 24 hours of first lesion appearance for all three cases. The young siblings received oral acyclovir 200 mg four times daily, while their immunocompetent mother received acyclovir 800 mg four times daily.



Figure 5. Feet of 2-year-old male showing reduced blister formation, lesion involution, and no new lesions



Figure 6. Palms of 2-year-old male showing involution of papules and no new lesions

All patients were followed with a clinical evaluation after one day of treatment and subsequently after three days of treatment. In the two young siblings, new lesions stopped appearing and most existing lesions showed noticeable involution after a single day of treatment, shown in [Figure 5](#) and [Figure 6](#). Significant reduction in pruritus and fever cessation were also noted at this time. Complete resolution was achieved with three days of acyclovir therapy. The single vesicle observed on their mother showed complete resolution after a single day of treatment.

3. Discussion

We present three cases of HFMD successfully treated with oral acyclovir to demonstrate the therapeutic role of acyclovir for symptomatic HFMD in young children and adults. Although HFMD is usually self-limited, the presence of fever and skin lesions can cause significant distress. Furthermore, patients are potentially contagious until skin lesions resolve, with peak infectivity being earlier in the disease course. Early initiation of oral acyclovir may shorten the disease course and halt progression of new skin lesions, thus limiting transmission and preventing outbreaks. The possibility that acyclovir did not alter the disease course at all in our patients should be considered. However, this is highly unlikely given the similar time course of resolution in all patients after intervention.

Younger children and immunocompromised adults are most susceptible [10]. Immunocompromised patients may display an unusually prolonged clinical course as described in recent literature [20]. Household disease transmission among family members occurs commonly, usually with children infected by an asymptomatic or mildly symptomatic adult [7,13]. Many cases of child-to-child and adult-to-child HFMD household transmission have been described [12]. To our knowledge, only a single case of child-to-adult transmission has been reported among the few reported cases in immunocompetent adults [8,10,13]. HFMD symptomatic transmission among immunocompetent adults is rare especially when caused by close contact with children, as we report.

To date, three studies have been reported in the current literature demonstrating the therapeutic benefit of acyclovir in HFMD. [11,14]. One study with twelve children ages 1 to 5 years and one adult with HFMD caused by CVA16 were treated with oral acyclovir (200-300 mg five times daily for five days) within 1 to 2 days of rash onset. All patients demonstrated significant therapeutic benefit within 24 hours of initiation with symptomatic relief and noticeable involution of lesions. Therapy was continued for five days by which time all mucocutaneous lesions were virtually gone, shortening natural disease course and severity [14]. In a second case report, an adult likely infected with CVA6 genotype presented with widespread hemorrhagic bullae and showed complete resolution after 7 days of IV acyclovir, used as refractory therapy. A third case reported an immunocompromised adult who presented with a prolonged symptomatic infection for over 3 weeks, which completely resolved after 5 days of acyclovir therapy [11].

The genome of enteroviruses does not encode for thymidine kinase, which is necessary for acyclovir activity. Taking this into consideration, acyclovir should not be effective in treating HFMD. While in vitro studies investigating the therapeutic mechanism of acyclovir in HFMD are lacking, it has been suggested that the therapeutic effects are likely due to acyclovir's ability to enhance the body's natural interferon (IFN) promoting antiviral response [14]. The role of IFN in treating HFMD has been supported by the use of recombinant human IFN- α 2b topical spray in a randomized, controlled clinical trial offering rapid symptomatic relief [15].

Specific antiviral therapies such as capsid inhibitors which impair viral attachment and uncoating have activity against many enteroviruses [16]. One in particular, pleconaril, showed less impressive outcomes in treating enteroviral meningitis in adults. The efficacy of pleconaril has not been definitively established and is unavailable for routine clinical use [17-19]. This drug has never been used in HFMD. Results from in vitro studies strongly support the role of pleconaril against enteroviruses [22,23]. However, in clinical practice, only acyclovir has been used successfully for HFMD. In another case report, oseltamivir used in a patient with HFMD resulted in rapid healing of skin lesions [20]. Following these results, authors proposed that the sialic acid link common to coxsackievirus and influenza A virus may be responsible for oseltamivir's therapeutic role in HFMD [21].

Newly emerging strains and non-classical patterns of transmission of HFMD have been reported in the literature [9,10,13]. Investigational drugs have shown only modest therapeutic benefit at best in the most severe forms of HFMD, mainly targeting its complications in subpopulations [18,19]. However, acyclovir, as reported in several cases, has successfully treated mild and severe forms of HFMD across multiple subgroups [11,14]. As no clinical trials have been conducted to validate its efficacy, clinicians remain skeptical and do not consider acyclovir as a potential therapy. We report the successful use of oral acyclovir therapy in treating HFMD in two young children and an adult. We report these cases to recognize the therapeutic benefit of acyclovir even in the mildest forms of HFMD. In the case of outbreaks, acyclovir should be

considered as it may offer benefit to the population at large, especially since it is widely available and affordable.

Conflicts of Interest

The authors report no conflict of interest.

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Compliance with Ethical Standards and Informed Consent

Informed consent was obtained for publication of this case report.

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