Hand, foot and mouth disease (HFMD), an acute viral illness caused by coxsackieviruses or enteroviruses, is predominantly encountered in children under 10 years of age. Although it is usually self-resolving, there are a few rare cases which have an extremely aggressive clinical presentation and need to be treated on a priority. Many affected children present with florid or unusual lesions; are highly febrile, with high irritability or listlessness; and also refuse to eat. Such cases could be considered as severe ones. With no specific effective antiviral available to tackle HFMD cases, acyclovir may be used in severe cases for its antiviral effect. We describe three such cases of HFMD in children, treated with oral acyclovir, with gratifying results.

Keywords: Acyclovir, hand, foot and mouth disease, severe

Case Reports

Case 1
A 1-year-old male child was brought by parents with complaints of multiple oral erosions over the palate. Palmoplantar surface showed oval-to-elongate-shaped vesicles along with involvement of thighs and buttocks. Within a period of 12 h, the vesicles rapidly progressed to involve almost the entire body and extremities [Figure 1a and b]. The child was admitted under the care of a pediatrician, and symptomatic and supportive therapy in the form of IV fluids and antipyretics was initiated. The child had no history of any cutaneous rashes. As the clinical presentation was typical of HFMD case, oral acyclovir suspension was started in a dose of 10 mg/kg/dose 4 times a day. This was continued for a total period of 7 days. Within 48 h of beginning the acyclovir therapy, there was a remarkable improvement in the clinical condition of the patient with crusting of vesicles and improvement of constitutional symptoms [Figure 1c and d].

Case 2
A 15-month-old female child was brought by parents with a history of fever, sore throat, and listlessness for 2 days.
Damle: Acyclovir in severe Hand-Foot-Mouth disease

Figure 1: (a) Papulovesicular eruptions on an erythematous base with few accompanying erosions present over the right arm. (b) Papulovesicular eruptions on an erythematous base with few accompanying erosions present over the right leg. (c) Crusted vesicles present over the right arm after starting acyclovir. (d) Healing crusted scales present over both the lower limbs.

This was followed by appearance of vesicles over the palms, elbows, and buttocks. The child subsequently developed bullae over both the soles, painful in nature, making the child irritable [Figure 2a and b]. The child also refused to feed due to ongoing symptoms which made the parents extremely anxious. Oral acyclovir was given in a dose of 10 mg/kg/dose 4 times a day. By the 3rd day, there was a significant improvement in the clinical status of the child. The child started to feed within 48 h of starting acyclovir. The bullae and vesicles almost dried up within 72 h [Figure 2c]. However, acyclovir was continued for a total duration of 7 days.

Case 3
A 2-year-old male child presented with extensive distribution of vesicles over the buttocks and lower limbs progressing to erosions and ulcerations. The child had typical oval-shaped vesicles on an erythematous base over the palms and soles. Oral examination revealed discrete erosions over the palate. The clinical condition of the patient deteriorated rapidly, worsened by the decreased food intake and accompanying high-grade fever. He was admitted under the care of a pediatrician for supportive treatment. In view of classical clinical features suggestive of HFMD, the child was started on oral acyclovir in a dose of 10 mg/kg/dose 4 times a day. This was continued for 7 days with a good response.

Discussion
HFMD is a relatively mild childhood viral disease caused by coxsackievirus A16 (CVA16) or HEV71 but may occasionally be caused by CVA 4–7, A9, A10, B1–3, and B5. This condition is known to occur as periodic outbreaks, with predilection for summer and early fall in temperate climates, but throughout the year in the tropics.[6] Although maximum number of cases occur in children under the age of 10 years, adult cases have also been reported in literature.[9] Usually, HFMD has a self-resolving course, although there are a few exceptional cases which have an extremely aggressive clinical presentation and need to be treated on a priority. Mathes et al. identified four morphologies that characterize the severe end of the spectrum of HFMD and distinguish it from classic HFMD: (1) widespread vesiculobullous and erosive lesions extending beyond the palms and soles, (2) an eczema herpeticum-like eruption termed “eczema coxsackium,” (3) an eruption similar to Gianotti–Crosti, and (4) a petechial or purpuric eruption.[9]

Currently, there is no specific effective antiviral available to tackle HFMD cases. Acyclovir, the most widely used antiviral drug, exerts its therapeutic effect by undergoing phosphorylation to be activated into acyclovir triphosphate.[10,11] This action is done first by thymidine kinase (present in viruses such as herpes simplex, herpes zoster, and Epstein–Barr virus) and consequently by cellular enzymes. The triphosphylated form of acyclovir inhibits viral DNA, resulting in irreversible inhibition of further viral DNA synthesis. Enteroviruses, however, lack thymidine kinase, and in vitro studies have failed to show any inhibitory effect of acyclovir on them.[12,13] Thus, acyclovir is believed to work in HFMD by modulating the patient’s own interferon for its antiviral effect.[14]

Shelley et al.[12] demonstrated the valuable therapeutic effect of acyclovir in 12 children and one adult with HFMD in 1996. These patients were treated with oral acyclovir (200–300 mg five times daily for 5 days) within 1–2 days of onset of the rash. Symptomatic relief, defervescence, and significant involution of lesions were seen within 24 h of starting acyclovir.

Other situations where it may be reasonable to consider treatment with oral acyclovir include in infants who generally have a more severe course and in severely symptomatic patients. Rarely, myocarditis, meningoitis, encephalitis, paralysis, or pulmonary edema can occur.[15,16] These serious complications and even death are much more likely to be associated with epidemics of HEV71 rather than CVA16 and may warrant oral acyclovir. Infection with coxsackie A16 has been associated, however, with fatal rhabdomyolysis and renal failure,[17] and with spontaneous abortion in the first trimester of pregnancy.[18]
Conclusion
In a resource-poor setting with no laboratory support to confirm the diagnosis, it would be worthwhile to consider acyclovir in the management of clinically diagnosed severe HFMD cases. However, multicenter, randomized, controlled studies for severe cases of HFMD are required for validating the role of acyclovir.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

References
1. Chatproedprai S, Theanboonlers A, Korkong S, Thongmee C, Wananukul S, Poovorawan Y, et al. Clinical and molecular characterization of hand-foot-and-mouth disease in Thailand, 2008-2009. Jpn J Infect Dis 2010;63:229-33.
2. Hagiwara A, Tagaya I, Yoneyama T. Epidemic of hand, foot and mouth disease associated with enterovirus 71 infection. Intervirology 1978;9:60-3.
3. Schmidt NJ, Lennette EH, Ho HH. An apparently new enterovirus isolated from patients with disease of the central nervous system. J Infect Dis 1974;129:304-9.
4. Zhu Z, Zhu S, Guo X, Wang J, Wang D, Yan D, et al. Retrospective seroepidemiology indicated that human enterovirus 71 and coxsackievirus A16 circulated wildly in central and Southern China before large-scale outbreaks from 2008. Virol J 2010;7:300.
5. Sasidharan CK, Sugathan P, Agarwal R, Khare S, Lal S, Jayaram Paniker CK, et al. Hand-foot-and-mouth disease in Calicut. Indian J Pediatr 2005;72:17-21.
6. Belazarian L, Lorenzo ME, Pearson AL, Sweeney SM, Wiss K. Exanthematous viral diseases. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick’s Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012. p. 2360-2.
7. World Health Organization. A Guide to Clinical Management and Public Health Response for Hand, Foot and Mouth Disease (HFMD). Public Health; 2011.
8. Shin JU, Oh SH, Lee JH. A case of hand-foot-mouth disease in an immunocompetent adult. Ann Dermatol 2010;22:216-8.
9. Mathes AE, Oza V, Ilona J, Cordoro KM, Yagi S, Howard R, et al. “Eczema Coxsackium” and unusual cutaneous findings in an enterovirus outbreak. Pediatrics 2013;132:e149-e157.
10. Evans TY, Tying SK. Advances in antiviral therapy in dermatology. Dermatol Clin 1998;16:409-19.
11. Wagstaff AJ, Faulds D, Goa KL, Cordoro KM, Yagi S, Howard R, et al. Aciclovir. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1994;47:153-205.
12. Shelley WB, Hashim M, Shelley ED. Acyclovir in the treatment of hand-foot-and-mouth disease. Cutis 1996;57:232-4.
13. Rawlinson WD. Antiviral agents for influenza, hepatitis C and herpesvirus, enterovirus and rhinovirus infections. Med J Aust 2001;175:112-6.
14. Faulkner CF, Godbolt AM, DeAmbrosis B, Triscott J. Hand, foot and mouth disease in an immunocompromised adult treated with aciclovir. Australas J Dermatol 2003;44:203-6.
15. Chang LY, Lin TY, Huang YC, Tsao KC, Shih SR, Kuo ML, et al. Comparison of enterovirus 71 and coxsackie-virus A16 clinical illnesses during the Taiwan enterovirus epidemic, 1998. Pediatr Infect Dis J 1999;18:1092-6.
16. Gilbert GL, Dickson KE, Waters MJ, Kennett ML, Land SA, Sneddon M, et al. Outbreak of enterovirus 71 infection in Victoria, Australia, with a high incidence of neurologic involvement. Pediatr Infect Dis J 1988;7:484-8.
17. Cooper DJ, Shaw DR, LaBrooy JT, Blumbergs P, Gilbert J, Simmons A, et al. Fatal rhabdomyolysis and renal failure associated with hand, foot and mouth disease. Med J Aust 1989;151:232-4.
18. OgilvieMM, TearneCF. Spontaneous abortion after hand-foot-and-mouth disease caused by coxsackie virus A16. Br Med J 1980;281:1527-8.