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Hand-Foot-and-Mouth Disease

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Introduction

Background

Hand-foot-and-mouth disease (HFMD) is a viral illness with a distinct clinical presentation of oral and characteristic distal extremity lesions. Most commonly, the etiologic agents are coxsackieviruses, members of the Picornaviridae family.

Pathophysiology

Epidemic hand-foot-and-mouth disease (HFMD) viral infections are usually caused by members of the Enterovirus genus, namely, coxsackievirus A16 or enterovirus 71. In addition, sporadic cases with coxsackievirus types A4-A7, A9, A10, B1-B3, and B5 have been reported. Infections usually occur as isolated events, but epidemics occur regularly. An outbreak of HFMD in China during 2003 was caused by echovirus 19.[1]

The incubation period averages 3-6 days. Coxsackievirus infection is highly contagious. During epidemics, the virus is spread by horizontal transmission from child to child and from mother to fetus. Transmission occurs by means of direct contact with nasal and/or oral secretions, fecal material, or aerosolized droplets in a fecal-oral or oral-oral route. Initial viral implantation in the buccal and ileal mucosa is followed by spread to lymph nodes within 24 hours. Viremia rapidly ensues, with spread to the oral mucosa and skin. By day 7, neutralizing antibody levels increase and the virus is eliminated.

Frequency

United States

HFMD epidemics tend to occur every 3 years in the United States.

International

Worldwide HFMD occurrences are reported. A seasonal pattern is present in temperate climates, with a peak incidence in late summer and early fall.

Mortality/Morbidity

- Hand-foot-and-mouth disease (HFMD) is more severe in infants and children than adults, but generally, the disease has a mild course.
- Enteroviral infections may also cause myocarditis, pneumonia, meningoencephalitis, and even death.
- Rarely, disease recurs.
- Infection in the first trimester may lead to spontaneous abortion or intrauterine growth retardation.
- A large outbreak of HFMD in Taiwan caused by enterovirus 71 had a high mortality rate of 19.3% in the severe cases; the deaths resulted from pulmonary hemorrhage. During this outbreak, mortality rates were highest in children younger than 3 years.[2]
- In a large epidermic (138 cases) of HFMD related to enterovirus 71 in Singapore, 7 fatalities occurred, most from interstitial pneumonitis or brainstem encephalitis. The report's conclusions were that in general, HFMD is a benign disease but the presence of unusual physical findings, elevated total white blood cell count, and vomiting and the absence of oral ulcers may signify a patient with higher risk of a fatal outcome.[3]
- A later study of an HFMD epidermic (14 children) in Australia, again with enterovirus 71, reported that 9 (64%)

developed severe neurologic disease in which the host immune response seemed to cause most of the neurologic manifestations.[4]

- In one study of an outbreak HFMD in Sarawak, Malaysia caused by human enterovirus 71, the authors identified 3 clinical risk factors to help detect children at risk for neurologic complications. Total duration of fever for 3 or more days, peak temperature elevation greater or equal to 38.5°C, and a history of lethargy all were independently associated with cerebrospinal fluid pleocytosis and neurologic disease.[5]

Race

No racial predilection is recognized for hand-foot-and-mouth disease.

Sex

The male-to-female ratio for hand-foot-and-mouth disease is 1:1.

Age

Most cases of hand-foot-and-mouth disease affect children younger than 10 years, although cases in adults are reported.

Clinical

History

A brief prodrome of 12-36 hours duration is part of the usual presentation of hand-foot-and-mouth disease (HFMD), which consists of the following:

- Low-grade fever with an average temperature of 38.3°C and duration of 2-3 days
- Anorexia
- Malaise
- Abdominal pain
- Sore mouth
- Cough

In one study, 80% of the children presented with anorexia and mouth soreness. The enanthem usually precedes the exanthem that is asymptomatic, but both may occur simultaneously. The lesions on the hands and feet are present for 5-10 days. The mucosal and cutaneous lesions heal spontaneously in 5-7 days.

Physical

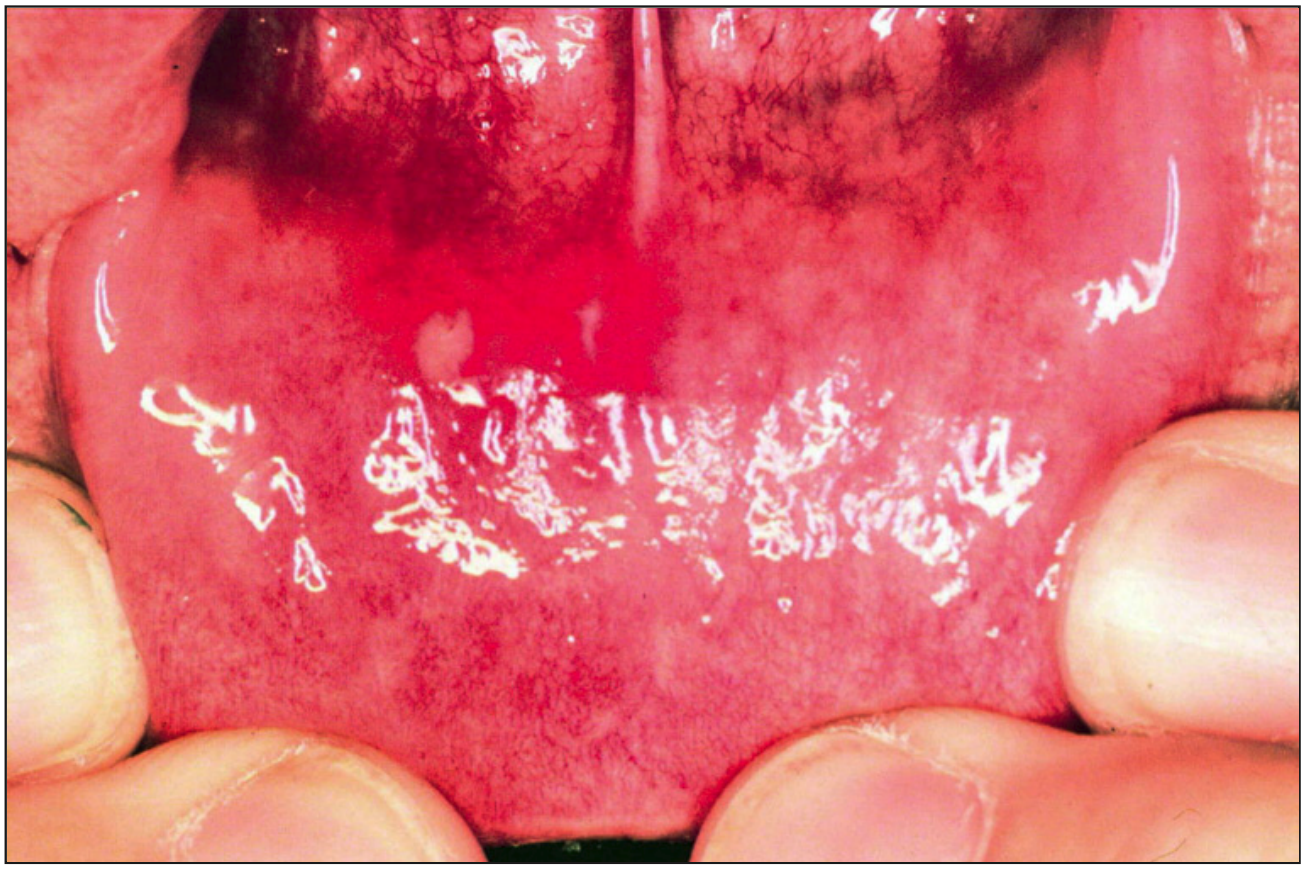
Hand-foot-and-mouth disease (HFMD) is more severe in infants and children than adults, but generally, the disease has a mild course. Symptoms such as malaise, low-grade fever, and anorexia are often present. Occasionally, patients have high fever, marked malaise, diarrhea, and arthralgias.

Enteroviral infections may also cause myocarditis, pneumonia, meningoencephalitis, and even death. Infection in the first trimester may lead to spontaneous abortion or intrauterine growth retardation.

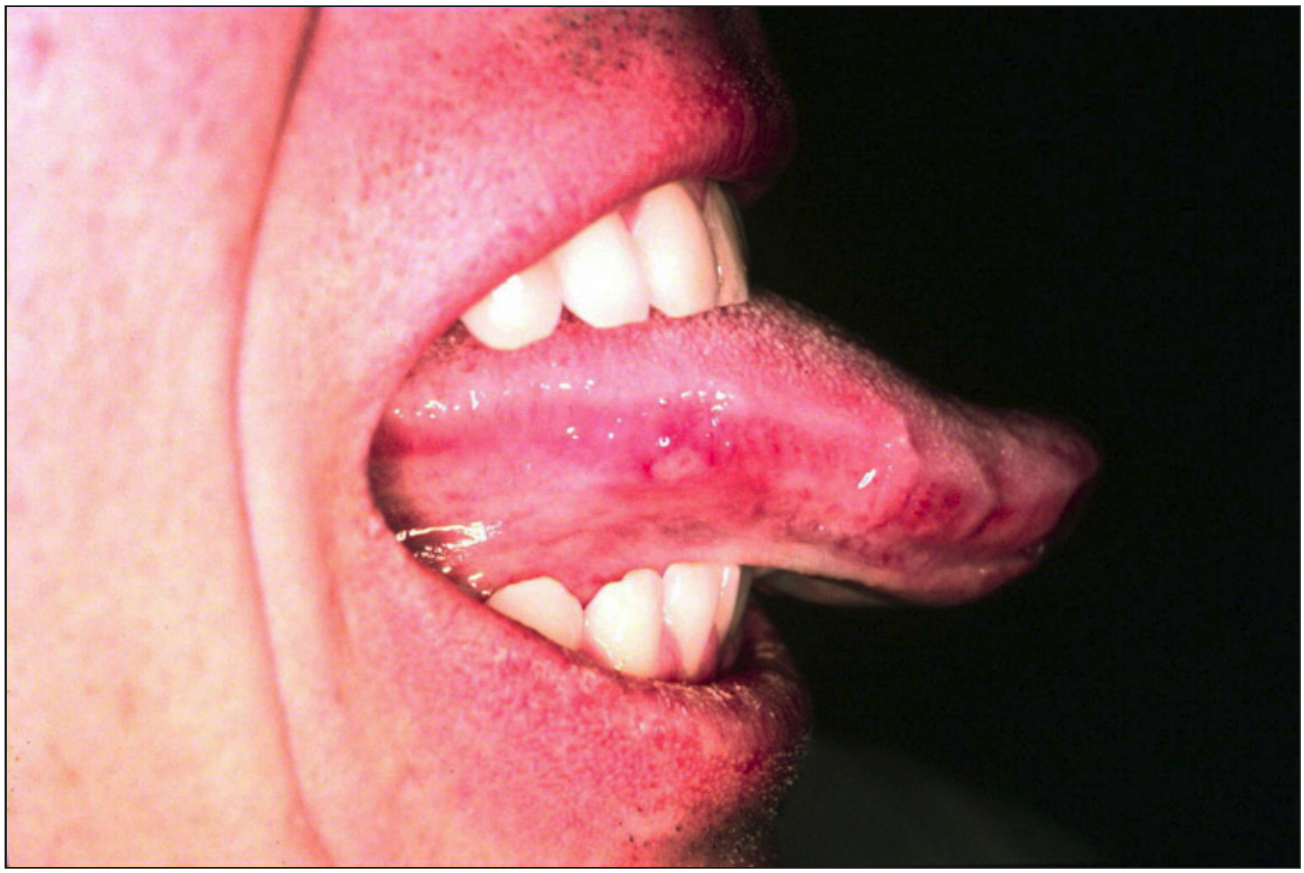
Rarely, disease recurs. One report describes a 15-year-old white boy with recurrent episodes of HFMD at 3 weeks and 7 months following the initial viral illness.[6] The lesions in the recurrent episodes were located in the same distribution as the initial presentation. His workup after the last case revealed an absence of immunodeficiency and a greater than 4-fold increase in coxsackievirus B titers. No serologic evidence of acute infection was identified, and titers of immunoglobulin G remained elevated for 1 year following this third episode.

Oral lesions begin as erythematous macules that evolve into 2-3 mm vesicles on an erythematous base. The vesicles are rarely observed because they rapidly become ulcerated. They are painful and may interfere with eating. The total number of ulcers averages 5-10. The vesicles may involve the palate, buccal mucosa, gingiva, and tongue. The tongue is involved

in 44% of the cases, and, in addition to the ulcers, the tongue may be edematous and tender. Note the images below.

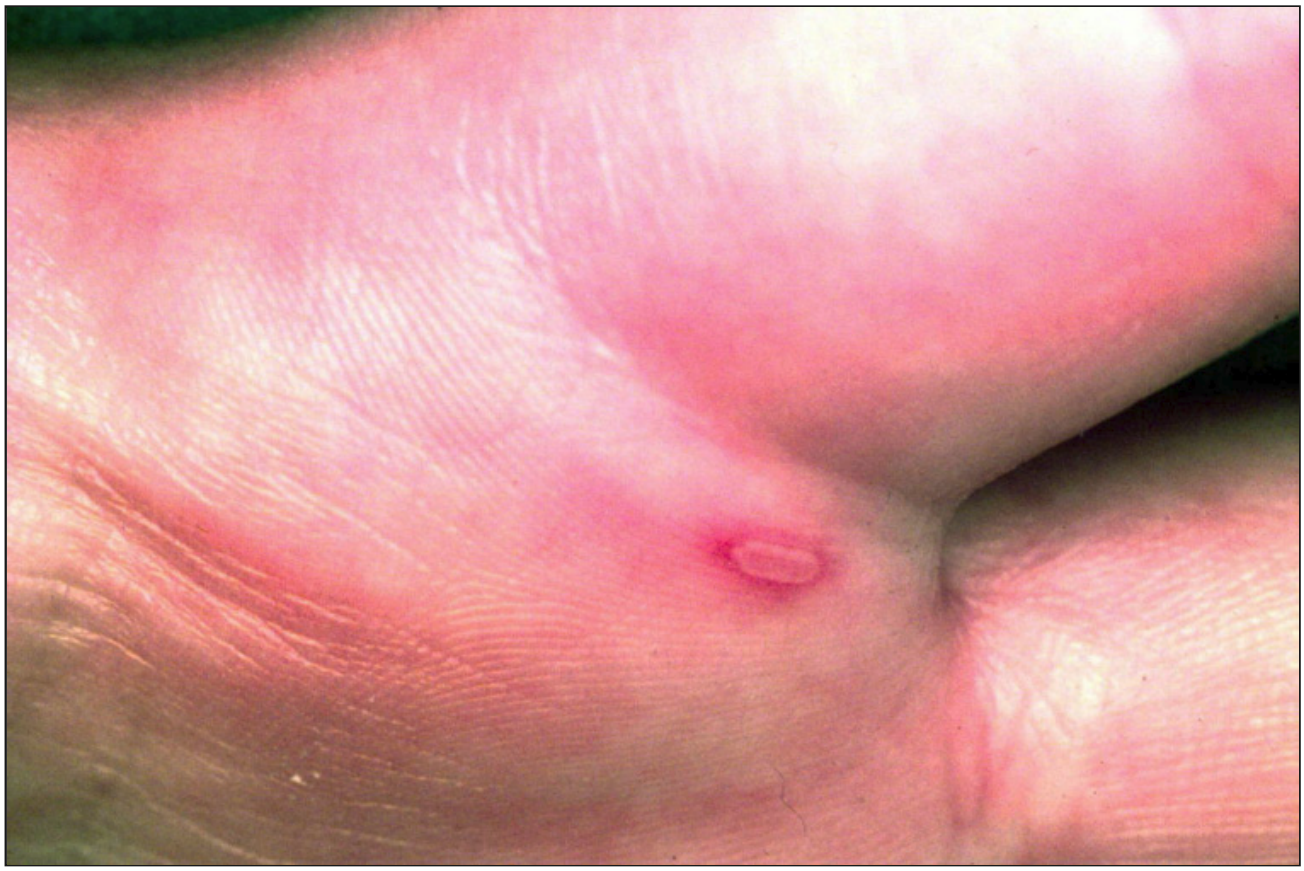


The lower lip has an ulcer with an erythematous halo.



The tongue has an ulcer with an erythematous halo.

Cutaneous lesions are characteristic and are present in two-thirds of patients. Typically, the hands, feet, and buttocks are involved. The hands are involved more often than the feet, and the dorsal aspect of the hands and sides of the fingers are more commonly involved than the palmar surfaces. Each lesion begins as a 2-10 mm erythematous macule on which a central, gray, oval vesicle develops. The lesions are characteristically elliptical; their long axis parallels the skin lines. These lesions are asymptomatic and resolve in 3-7 days as a result of fluid resorption. Note the image below. Erythematous maculopapular eruptions may also occur on the buttocks and arms. In one report, 22% of the patients also had marked cervical or submandibular lymphadenopathy.



A typical cutaneous lesion has an elliptical vesicle surrounded by an erythematous halo. The long axis of the lesion is oriented along the skin lines.

Causes

Epidemic hand-foot-and-mouth disease (HFMD) infections are usually caused by coxsackievirus A16 or enterovirus 71.[7] In addition, sporadic cases with coxsackievirus types A4-A7, A9, A10, B1-B3, and B5 are reported. An outbreak of hand-foot-and-mouth disease in China during 2003 was caused by echovirus 19.[1]

Differential Diagnoses

Aphthous Stomatitis
Chickenpox
Erythema Multiforme
Herpes Simplex

Other Problems to Be Considered

Herpangina

Workup

Laboratory Studies

- Generally, no laboratory studies are necessary for hand-foot-and-mouth disease (HFMD). Leukocyte counts are 4000-16,000/µL. Occasionally, atypical lymphocytes are present.
- The virus can be isolated from swabs of the vesicles or mucosal surfaces or from stool specimens and then inoculated into mice or cultured on viral tissue media.

- Neutralizing antibodies rapidly disappear; thus, they are usually detectable only in the acute phase.
- High levels of complement-fixing antibodies are present in the convalescent phase.
- Studies have illustrated the usefulness of a molecular assay using polymerase chain reaction primers to arrive at a rapid and specific diagnosis in order to distinguish between coxsackievirus A16 and enterovirus 71.[8] This may hold promise in future outbreaks because infections with enterovirus 71 tend to be associated with more severe complications and fatalities. One study suggests that swabs be collected within 4 days of HFMD onset to increase diagnostic yield.[9]

Histologic Findings

Classic histopathologic findings of hand-foot-and-mouth disease (HFMD) include an intra-epidermal vesicle that contains neutrophils and eosinophilic cellular debris. The adjacent epidermis has reticular degeneration, that is, intercellular and intracellular edema. The dermis has a mixed infiltrate. Eosinophilic intranuclear inclusions are observed with electron microscopic studies.

Neuropathology in fatal cases of enterovirus 71 infection have shown features of an acute encephalitis involving the brain stem and spinal cord.[10]

Treatment

Medical Care

Usually, no medical care is necessary for hand-foot-and-mouth disease (HFMD).

Medication

The topical application of anesthetics is beneficial. Viscous lidocaine, dyclonine solution, or diphenhydramine (Benadryl) may be used to treat painful oral ulcers. Antipyretics may be used to manage fever, and analgesics may be used to treat arthralgias.

A case report of severe hand-foot-and-mouth disease (HFMD) from enterovirus infection in an immunocompromised patient described a faster resolution of symptoms and lesions with oral acyclovir.[11] Low-level laser therapy has also been shown to shorten the duration of painful oral ulcers.[12]

Anesthetic agents, topical

These agents provide symptomatic relief of pain as a result of mucosal lesions.

Dyclonine (Dyclone)

Topical anesthetic available in a solution, spray, or lozenge. Affects cell membrane permeability and blocks impulses at peripheral nerve endings in the skin.

Dosing

Adult

Apply 0.5% or 1% solution to ulcers q2h prn pain; not to exceed 200 mg, or 40 mL of 0.5% solution or 20 mL of 1% solution

Pediatric

Administer as in adults; adjust for body weight

Interactions

Coadministration with St. John's wort may cause an increased risk of cardiovascular collapse and/or delayed emergence from anesthesia

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Severe shock, AV heart block, or central nervous system depression or excitation possible with overdosing; may increase risk of aspiration (impairs swallowing); caution in shock or heart block

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Viscous lidocaine (Dilocaine; DermaFlex Gel)

Topical anesthetic. Decreases permeability to sodium ions in neuronal membranes and results in inhibition of depolarization, blocking transmission of nerve impulses.

Dosing

Adult

Apply to oral ulcers with cotton-tip applicator prn pain

Pediatric

Administer as in adults; adjust for body weight

Interactions

Coadministration with cimetidine or beta-blockers increases toxicity; coadministration with procainamide and tocainide may result in additive cardiodepressant action; may increase effects of succinylcholine

Contraindications

Documented hypersensitivity; Adams-Stokes syndrome and Wolf-Parkinson-White syndrome; severe sinoatrial, AV, or intraventricular block (if artificial pacemaker is not used)

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Complete anesthesia of mouth and pharynx with possible choking on food and aspiration and biting of tongue or buccal mucosa; overdose may cause toxicity (lightheadedness, euphoria, tinnitus, nausea, vomiting, seizures, coma, bradycardia, hypotension, cardiac arrest)

Antihistamines

Antihistamines act by means of the competitive inhibition of histamine at the H1 receptor. This effect mediates wheal and flare reactions, bronchial constriction, mucous secretion, smooth muscle contraction, edema, hypotension, CNS depression, and cardiac arrhythmias.

Diphenhydramine (Benadryl, Benylin, Diphen, AllerMax)

Ethanolamine class, histamine receptor type 1 blocker. Has significant anticholinergic and sedative properties that causes some degree of topical anesthesia by impairing the transmission of nerve impulses.

Dosing

Adult

Symptomatic pain control of oral ulcers: Combine in cocktail or elixir with aluminum and magnesium hydroxide (Mylanta), viscous lidocaine and/or sucralfate (Carafate); swish and spit out several times qd prn pain

Pediatric

Administer as in adults; adjust for body weight

Interactions

Potentiates effect of CNS depressants; do not give syrup with medications that can cause disulfiramlike reactions (due to alcohol content); may also interact with tricyclic antidepressants, MAOIs, antimuscarinics, amantadine, and procainamide

Contraindications

Documented hypersensitivity; MAOIs

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Xerostomia; may exacerbate angle-closure glaucoma, hyperthyroidism, peptic ulcer, and urinary tract obstruction, GI obstruction, hepatic disease, ileus, prostatic hypertrophy, and COPD

Antacid/antiulcer agents

These agents are used for the symptomatic treatment of acid-induced gastritis and the treatment of GI ulcers.

Sucralfate (Carafate)

Aluminum complex antacid that may help in the treatment of oral mucosal ulcerations. Similar to its effects on GI ulcers, sucralfate forms a viscous adhesive substance that protects the GI lining against pepsin, peptic acid, and bile salts. Binds and covers the ulcer, promoting healing.

Dosing

Adult

Symptomatic pain control for oral ulcers: Combine in cocktail or elixir with aluminum and magnesium hydroxide (Mylanta), viscous lidocaine and diphenhydramine; swish and spit out several times qd prn pain

Pediatric

Administer as in adults; adjust for body weight

Interactions

May decrease effects of ketoconazole, ciprofloxacin, tetracycline, phenytoin, warfarin, quinidine, theophylline, and norfloxacin; antacids, reduces H2 blockers, digoxin, lansoprazole, levothyroxine, phenytoin, and theophylline absorption

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure and conditions that impair excretion of absorbed aluminum; high aluminum levels possible, especially if used with aluminum-containing antacids

Aluminum hydroxide, magnesium hydroxide, simethicone (Mylanta)

Lowers gastric pH and covers ulcer bases. Similar to its effect on GI ulcers, may cover the ulcer base, allowing more rapid healing. Magnesium and/or aluminum antacid mixtures are used to prevent bowel function changes.

Dosing

Adult

Symptomatic pain control for oral ulcers: Combine in a cocktail or elixir with viscous lidocaine, diphenhydramine and/or sucralfate; swish and spit out several times daily prn pain

Pediatric

Administer as in adults; adjust for body weight

Interactions

Reduces efficacy of fluoroquinolones, corticosteroids, benzodiazepines, and phenothiazines; aluminum and magnesium potentiate effects of valproic acid, sulfonylureas, quinidine, and levodopa

Contraindications

Documented hypersensitivity; renal impairment may lead to high aluminum levels and further osteomalacia

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in severe renal impairment and recent massive upper GI hemorrhage

Follow-up

Inpatient & Outpatient Medications

- For symptomatic pain control for oral ulcers associated with hand-foot-and-mouth disease (HFMD), elixirs such as diphenhydramine (Benadryl), aluminum and magnesium hydroxide (Mylanta), and sucralfate (Carafate) can be helpful. Several times daily, the patient should swish the elixir in his or her mouth and spit it out.
- The application of topical viscous lidocaine with a cotton-tipped swab several times daily can help in controlling the pain caused by oral ulcers.

Complications

- Dehydration occasionally occurs in children with hand-foot-and-mouth disease.
- Rarely, complications of hand-foot-and-mouth disease include meningoencephalitis, myocarditis, pulmonary edema, and death.

Prognosis

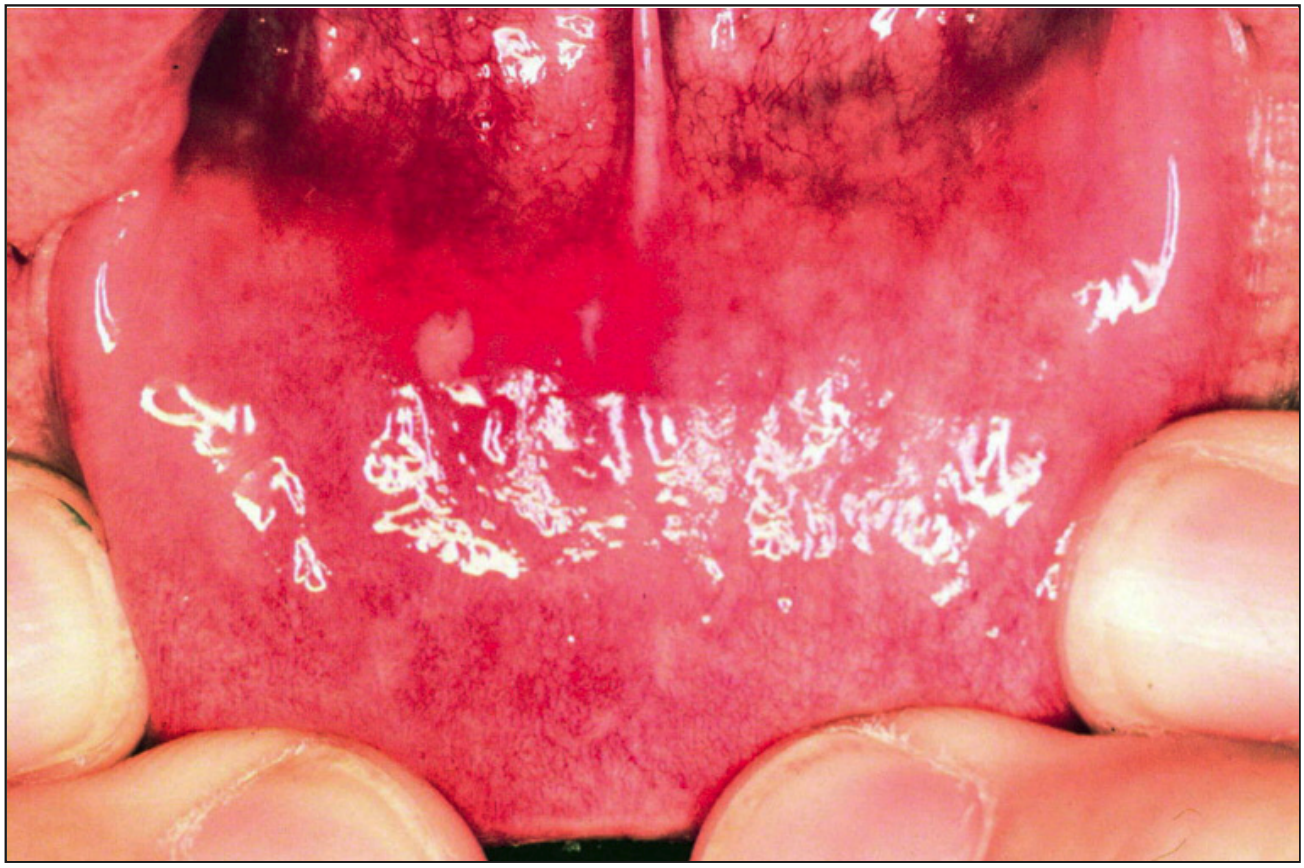
- The prognosis for hand-foot-and-mouth disease is excellent; except in large epidemics caused by human

enterovirus 71 in which neurologic complications and death have been reported, especially in children.

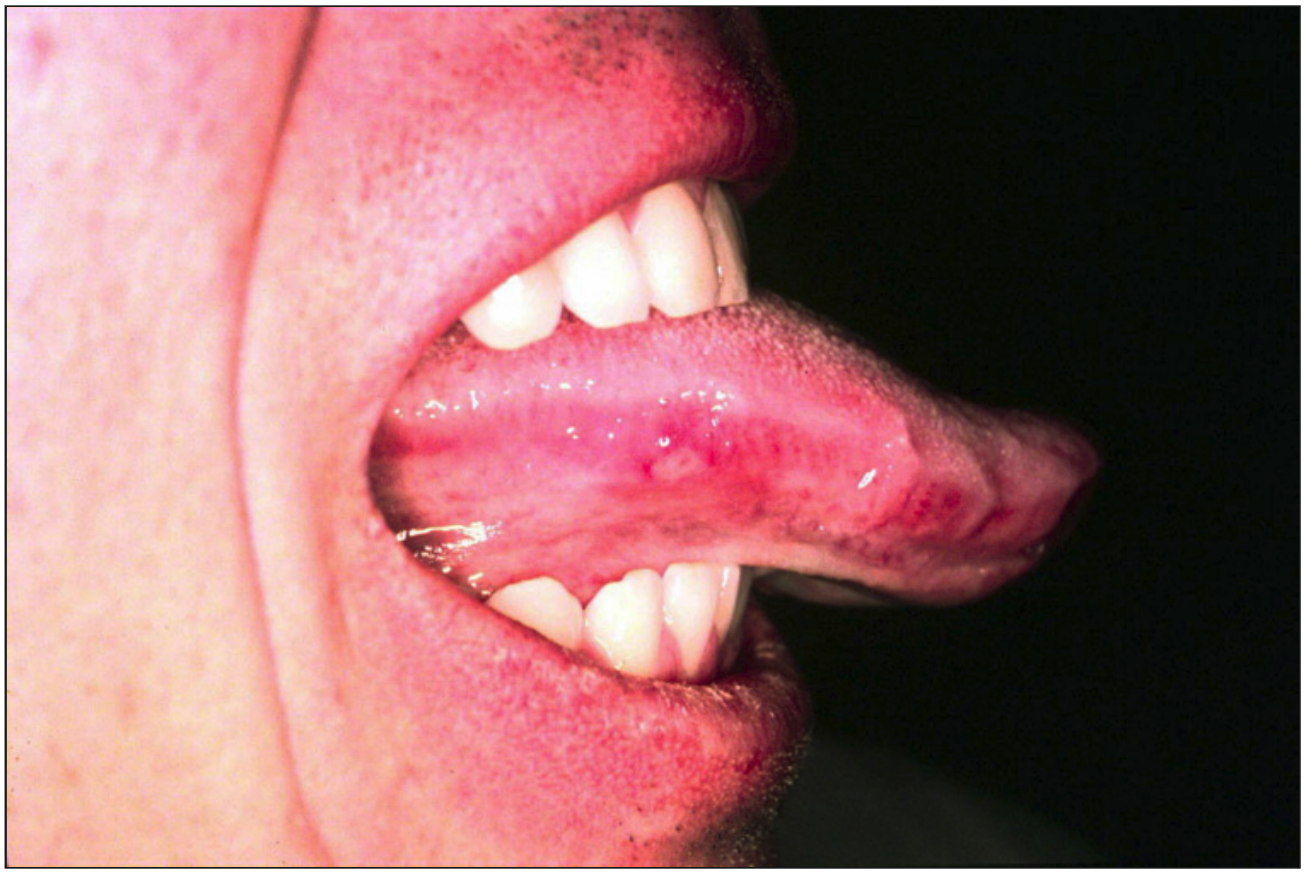
Patient Education

- The virus that causes hand-foot-and-mouth disease may be present in the patient's stool for 1 month.
- The patient's exclusion from school is generally not required.
- Good hand-washing technique is necessary to reduce the potential spread of disease.
- To reduce viral spreading, do no rupture blisters.

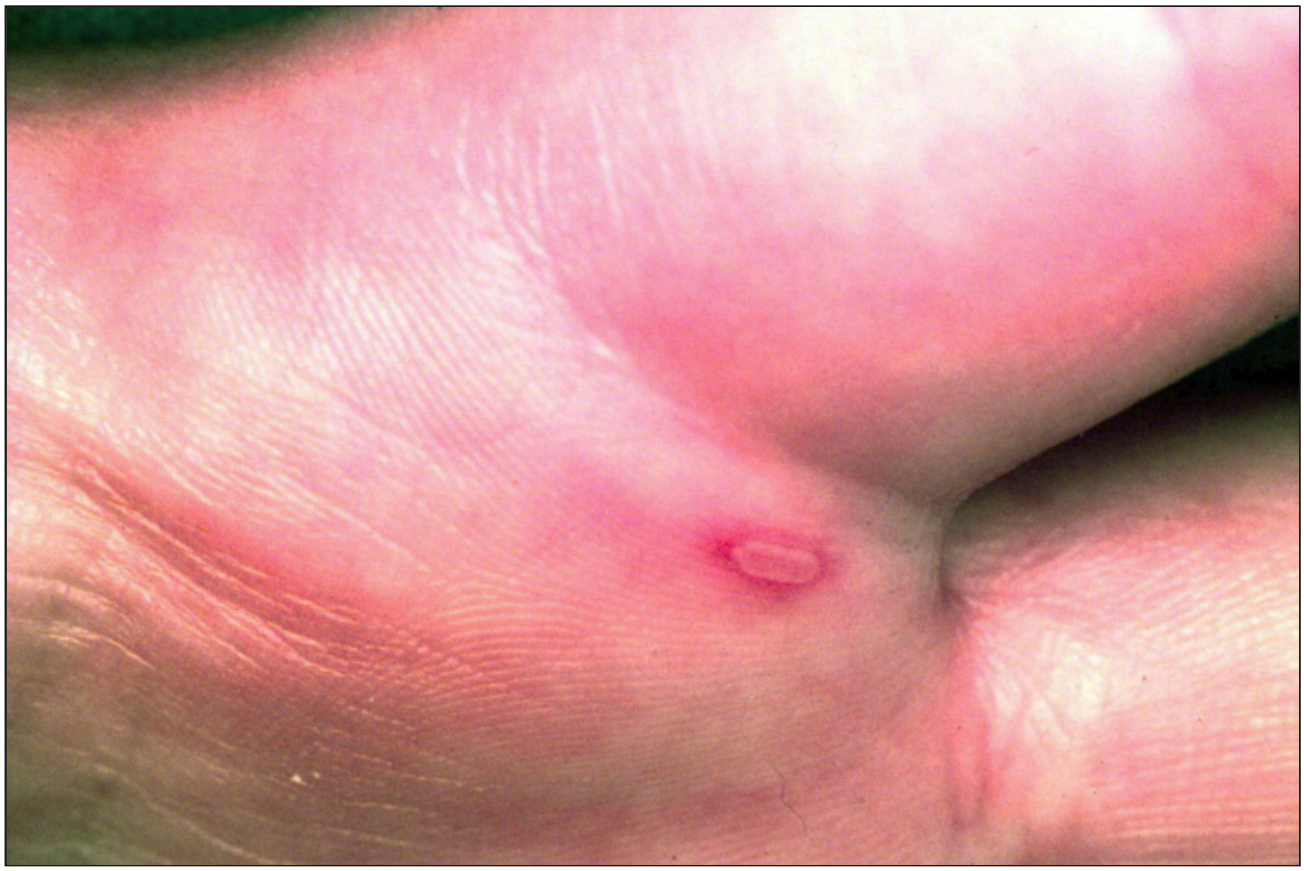
Multimedia



Media file 1: The lower lip has an ulcer with an erythematous halo.



Media file 2: The tongue has an ulcer with an erythematous halo.



Media file 3: A typical cutaneous lesion has an elliptical vesicle surrounded by an erythematous halo. The long axis of the lesion is oriented along the skin lines.

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Keywords

hand-foot-and-mouth disease, HFMD, Enterovirus infection, coxsackievirus A16, enterovirus 71, coxsackievirus A4-A7, coxsackievirus A9, coxsackievirus A10, coxsackievirus B1-B3, coxsackievirus B5, myocarditis, pneumonia, meningoencephalitis, erythematous macule, erythematous maculopapular eruptions, cervical lymphadenopathy, submandibular lymphadenopathy

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