DENTINO
JURNAL KEDOKTERAN GIGI
Vol VI. No 1. Maret 2021

MANAGEMENT OF HSV-1 AND HSV-2 PRIMARY INFECTION IN ADULT PATIENT: A CASE REPORT

Bima Ewando Kaban[1)], Dahlia Riyanto[2)], Adiastuti Parmadiati[3)], Desiana Radithia[4)], Bagus Soebadi[5)]
[1)] Resident of Oral Medicine Specialist Programme, Faculty of Dental Medicine, Universitas Airlangga
[2)] Resident of Oral Medicine Specialist Programme, Faculty of Dental Medicine, Universitas Airlangga
[3)] Lecturer of Oral Medicine Department, Faculty of Dental Medicine, Universitas Airlangga
[4)] Lecturer of Oral Medicine Department, Faculty of Dental Medicine, Universitas Airlangga
[5)] Lecturer of Oral Medicine Department, Faculty of Dental Medicine, Universitas Airlangga

ABSTRACT
Infection of Herpes Simplex Virus (HSV) type 1 and 2 causes medical problems throughout the world. HSV-1 infection often affects the oral regions and HSV-2 infection is the most prevalent cause of genital ulcerations. It is possible for HSV-2 to cause oro-labial herpes and HSV-1 to cause genital herpes. Primary HSV infection usually affects children or adolescent, whereas adults usually experience infection more frequently due to viral reactivation. **Objective:** To discuss the management of Primary HSV-1 and HSV-2 Infection which appears simultaneously in adults. **Case report:** a 33-year-old female patient came to hospital with multiple painful ulcers in her tongue, buccal and labial mucosa, preceded by prodrome, followed with eruption and outbreak of vesicles on her skin. The first laboratory examination confirmed a high titer of reactive Immunoglobulin M (IgM) of anti-HSV-1 and Immunoglobulin M (IgM) anti-HSV-2. She was diagnosed to have Primary HSV-1 and HSV-2 Infection and treated with oral Acyclovir and Chlorine dioxide mouthwash with good healing. The clinical presentation, differential diagnosis and management of primary herpetic stomatitis are discussed. **Conclusion:** Correct diagnosis and treatment can restore well-being, avoid secondary problems for patients, and prevent the use of inappropriate drugs.

Keywords **:** Herpes Simplex Virus, HSV-1, HSV-2, Management, Primary Herpes Infection
Correspondence: Bima Ewando Kaban. Jl. Mayjen Prof. Dr. Moestopo No.47, Pacar Kembang, Kec. Tambaksari, Kota SBY, Jawa Timur 60132. E-mail: drgbima.bk@gmail.com

INTRODUCTION

Primary herpes simplex infection is a primary infection disease caused by the herpes simplex virus 1 (HSV-1) and rarely caused by the herpes simplex virus 2 (HSV-2). HSV-1 has a greater tendency regarding the head, neck, oral, and perioral, spread mainly through active lesions and saliva. HSV-2 is more associated with lesions in the genital area. Primary herpes infection usually occurs during childhood with symptoms such as fever, cervical lymphadenopathy, headache, and the presence of several small vesicles that develop ulceration in the oral cavity and perioral area. The incidence of primary infection in adult patients is rare[,1,2]. So that this case report describes the management of primary HSV-1 and HSV-2 infection in adult patient.

CASE

A 33-year-old female patient came to Airlangga University Dental Hospital on March 26, 2019, with chief complaint of painful ulcers in her tongue, buccal mucosa, and labial mucosa in the last one day ago. The patient has had a fever 3 days before the ulcers occured. Red spots appeared on the patient's body since 1 day ago. The patient claimed to take acyclovir 2 times a day at night and morning, and paracetamol to relieve fever. The patient claimed that the fever was decreased but there was no change in her ulcers and red spots after taking the drugs. This condition has never been experienced before. Patients claimed to rarely experience ulcers The ulcer has never been treated and recovered in 7 days. None of the patient's family members had a history of the similar condition. The patient claimed to have no history of alergy. The patient works in the pub at night until early morning.

On extra-oral examination, numerous round papules with clear boundaries, regular margins and redness were found. In addition, there were pain in cheeks, arms, back and chest. There were brown, multiple, clearly demarcated, irregular edges crusts on the back and chest (Figure 1a). While on the lower lip, there were solitary, brown, clearly demarcated, and irregular edges crusts.

On intra-oral examination, there were multiple ulcers, round, varied in size, white with erythematous halo, clear borders, irregular edges, and pain in the buccal and tongue mucosa. Then, on the lower labial mucosa, there were multiple pseudomembranous appearance, white, clear borders, irregular edges, can be scrapped, and does not cause pain. (Figure 1b).

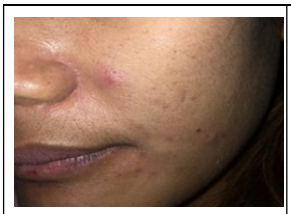
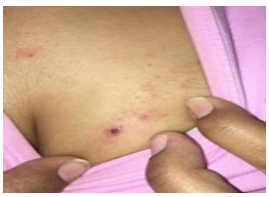
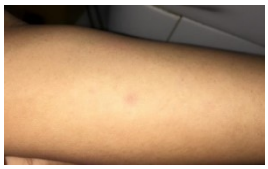
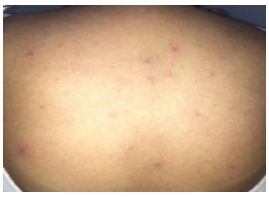





Figure 1a. Extra-oral Manifestation of HSV infection (first visit)

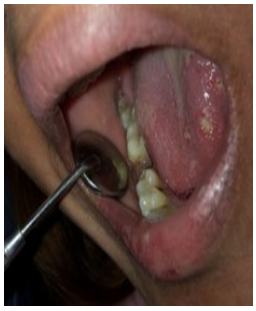
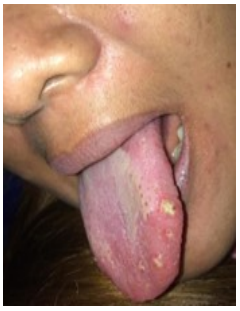
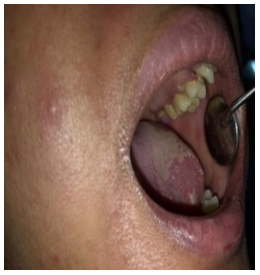
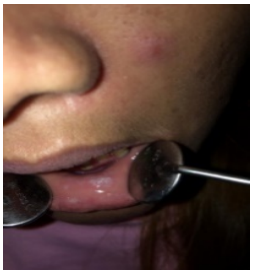





Figure 1b. Intra-oral manifestation of HSV infection (first visit)

MANAGEMENT OF CASE

First Visit

At this visit, the working diagnosis was suspected Intra Oral Herpes. The chair-side treatment included debridement and administration of mouthwash containing chlorine dioxide, then prescribed chlorine dioxide mouthwash to be used 4 times a day. Patients were also given communication, information, education (CIE), such as using mouthwash as recommended, adequate hydration, eating nutritious food, adequate rest, and maintaining oral hygiene. Planning at this visit included CBC, anti-HSV-1 Ig-M and Ig-G, and anti-HSV-2 Ig-M and Ig G examinations. The differential diagnosis in this case was Primary Herpes Simplex Infection and Hand Foot Mouth Disease (HFMD).

Second Visit (4 days after first visit)

The patient claimed the pain of her ulcers was decreased. She used the mouthwash as prescribed 4 times a day and maintain her oral hygiene. On intra-oral examination, a single, round, white ulcer with erythematous margins, clear borders, irregular margins, and pain was found in the upper labial mucosa. While on the tongue, there were multiple round ulcers, varying in size, white with erythematous halo, clear borders, irregular edges, and pain. On the lower labial mucosa, there are multiple erosions, red, clear borders, irregular edges, painless. The results of the second visit intra

oral examination were better than the first visit (Figure 2).

Laboratory tests showed reactive results on anti-HSV-1 and anti-HSV-2 Ig-M, while anti-HSV-1 and anti-HSV-2 Ig-G were not reactive. At this visit, the final diagnosis was confirmed, which is Primary HSV-1 and HSV-2 Infection. Chair-side treatments given to patients are debridement, administration of mouthwash containing chlorine dioxide, prescription Acyclovir 400 mg 5 times a day. In addition, CIE is given in the form of instructions to continue previous therapy using mouthwash as recommended, consume antiviral drugs as recommended, adequate hydration, eat nutritious food, get adequate rest, separate the patient from other family members, maintain oral hygiene, and do not do sexual intercourse until declared cured by a doctor. The patient was referred to a dermatologist for treatment of skin lesions.

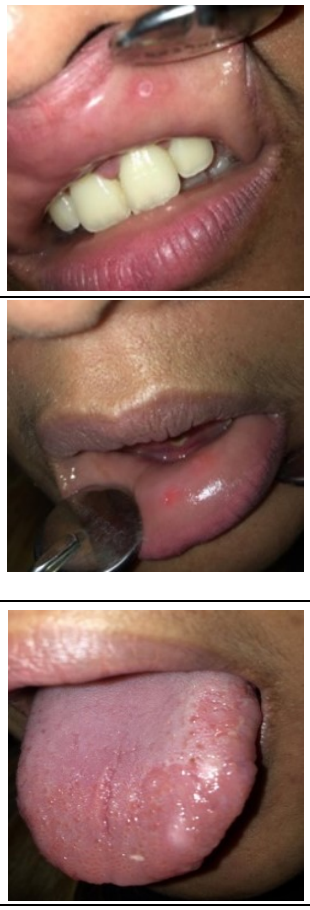


Figure 2. Development of oral manifestations of HSV infection after 4 days of treatment (second visit)

Third Visit (8 days after first visit)

The patient claimed her ulcers was painless. She used the mouthwash as prescribed 4 times a day and maintain her oral hygiene. The condition of the oral cavity showed improvement, but still found macules, single, round, diffuse borders, irregular edges, painless on the upper labial mucosa (Figure 3). On this visit, the final diagnosis was Primary Herpes Simplex Infection, with improved healing of the lesion. CIE were given to patient in the form of instructions to continue previous therapy, namely using mouthwash and taking antivirals as recommended, adequate hydration, eating nutritious food, adequate rest, and maintaining oral hygiene.

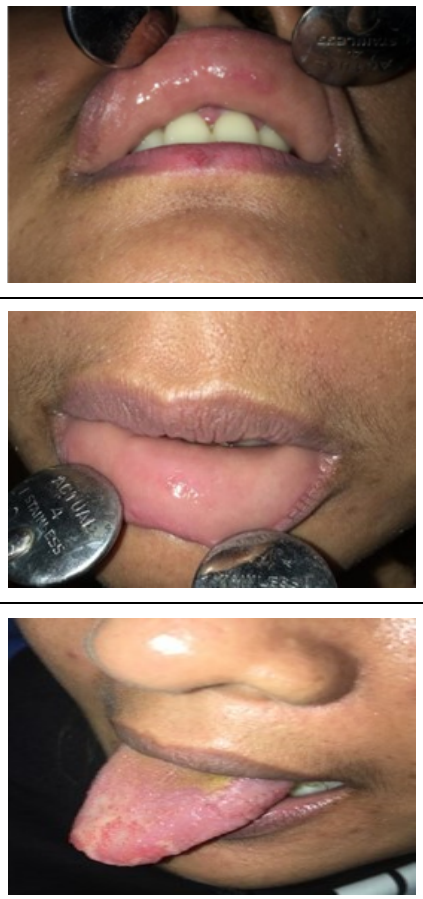
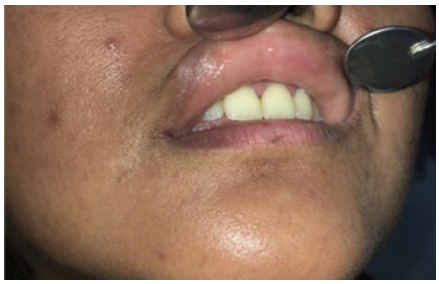
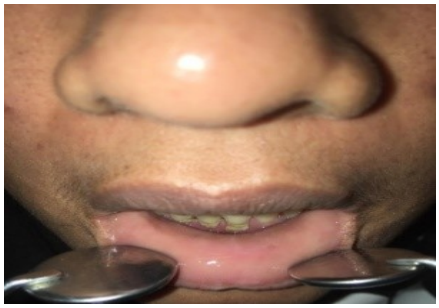


Figure 3. Development of oral manifestations of HSV infection after 8 days of treatment (third visit)

Fourth Visit (11 days after first visit)

After ten days of treatment, the patient claimed the ulcers on the lips and tongue had healed (figure 4). There were no ulcers or erosions on the mucosa of the upper and lower lips and tongue on intra-oral examination. The working diagnosis concluded that the primary herpes simplex infection was cured. The CIE that were provided includes stopping treatment, eating nutritious food, getting adequate rest and returning if there are still complaints in the oral cavity.





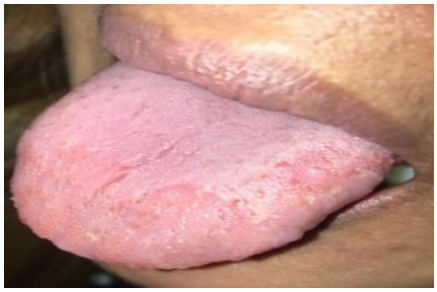


Figure 4. Development of oral manifestations by collaboration management between dermatologist and oral medicine specialist to treat HSV infection after 11 days (fourth visit)

DISCUSSION

Primary herpes simplex infection generally occurs in childhood, between the ages of 6 months and 5 years and the second peak occurs in the early 20s. Although onset is more common in children and young adults, primary infections are sometimes seen in people who are much older [3].

The diagnosis is usually made based on clinical features and history of the disease. In this case, the clinical features is multiple ulcers on the tongue surrounded by erythema and, previously, there is a prodromal symptom of fever and headache. The presence of prodromal symptoms is thought to be caused by the start of viral replication at the sensory nerve endings and in the epidermis or mucosa. The diagnosis can be confirmed through laboratory tests: serological tests (anti-HSV IgM and IgG), Tzanck test and immunofluorescence, but culture of viral isolates is still considered the gold standard. The HSV antibody test can detect both types of virus HSV-1 and HSV-2. Primary HSV infection is associated with an increase in IgM titer followed several weeks later by permanent IgG titer. People with new infections are more likely to test positive for herpes IgG and IgM or herpes IgM alone. In this case, the patient underwent anti-HSV-1 and anti-HSV-2 serological tests, showed reactive results in anti-HSV-1 and anti-HSV-2 IgM while non reactive in anti-HSV-1 and anti-HSV-2 IgG [3,4].

HSV is a virus that can cause oral mucosal disease. Humans are the only natural reservoir of HSV infection. HSV is short-lived on the outer surface of the body so the transmission of the virus must be through direct contact with infected lesions or body fluids, such as vesicle, saliva, and genital exudates. In addition, the virus must come into contact with the mucosa or skin that has lost integrity. The severity of the primary infection depends on the level of viral replication and the host's response to foreign pathogens [3].

After exposure, virions attach to host cells mediated by proteins in the viral envelope binding to specific receptors on the host cell membrane, namely the Herpes Virus Entry Mediator (HVEM) which is a member of the TNF receptor family; nectin-1 and nectin-2, a member of the immunoglobulin family; and specific site in HS generated by certain 3-O - sulfotransferase (HS 3-OS). After the virus enters the cytoplasm, the viral capsid protein is lost through a process known as un-coating and the viral nucleic acid is transported into the nucleus of the host cell. In the host cell nucleus, the viral genome is replicated. Replication requires protein kinase-dependent nucleoside triphosphates which are incorporated in the new viral genome by virus polymerase. In the next step, the new viral genome is transcribed into mRNA, which then translocated to the ribosome of the host cell. Viral proteins are synthesized by the host cell ribosomes assembled with duplicate viral genomes. Assembly is followed by maturation, an important process for newly formed virions to become infectious[5].

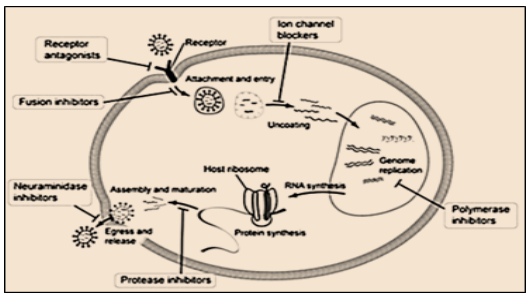


Figure 5. Pathogenesis of Herpes Simplex Virus [5,11]

The final cytopathogenic effect of HSV-1 and HSV-2 infection is characterized by the disintegration of host epithelial cells and the escape of viral infection into the extracellular environment. The new virus synthesis, in turn, can infect other epithelial cells or enter sensory nerve endings [5,11,12].

Herpes Simplex viruses is latent in the trigeminal nerve ganglion, where the maxillary division of the trigeminal nerve is a sensory branch that supplies the skin to the middle part of the face, under the eyelids, sides of the nose, upper lip, mucous membranes of the nasopharynx, maxillary sinuses, soft palate, and teeth. One of its terminal branches is the large palatal nerve that supplies the hard palate, which is keratinized mucosa, part of the maxillary gingiva, uvula, and part of the soft palate. The other branch is the superior alveolar nerve, which supplies the maxillary gingiva, teeth, and cheek membrane mucosa. HSV-1 causes fluid-filled bubbles (vesicles) in the area. This is what can differentiate the type of lesion due to viral infection from other ulcerated lesions where the lesion caused by viral infection can affect the keratinized mucosa [6,13].

Risk factors for acquiring HSV-2 infection revolve around direct exposure to fluids (i.e., saliva) from a seropositive individual containing viral products most often during sexual intercourse. HSV-2 is mainly transmitted through sexual intercourse [1,5,7]. In this case, the patient worked at the night club until the early hours of the morning and after a more detailed history taking, the patient admitted that he always felt tired after work and often engaged in sexual activity by changing partners. This can be considered as a predisposing factor for the patient to be infected with the HSV-1 and HSV-2 viruses.

In this case, the differential diagnosis were eliminated by analyzing a complete blood count and serologic examinations of anti-HSV-1, HSV-2 IgM and IgG. The results of laboratory tests confirmed the presence of the Herpes Simplex virus types 1 and 2 in the patient [5,7,11].

After primary mucocutaneous infection, HSV-1 and HSV-2 enter the sensory nerve endings and are carried via axonal retrograde transport to regional sensory ganglia where they establish a latent phase in the nerve cell body. It is in this latent phase that HSV remains in the non-replication phase. During the latent stage, herpes DNA can be detected, but does not produce viral protein. The most frequent latency site for HSV-1 is the trigeminal ganglion and for HSV-2 is the lumbosacral ganglia. Latent virus reactivation occurs when HSV switches to replication conditions; this can occur due to several factors, such as injury to peripheral tissue from trauma or sunburn, fever, immune suppression due to psychological stress, fatigue, menstruation, administration of corticosteroids, nerve damage, and altered antiviral activity in saliva.[3,5,9,13,14].

The recommended treatment for acute herpes infection if the disease is diagnosed early is systemic antiviral therapy to speed up clinical resolution. Administration of systemic acyclovir accelerates viral load resolution, healing time, and reduces pain. Acyclovir is generally well tolerated. Acyclovir has the unique property of being a selective inhibitor of herpes simplex virus repliation. Acyclovir triphosphate acts as both a substrate for and an inhibitor of viral DNA polymerase, thus blocking DNA synthesis. Acyclovir monophosphate is then further phosphorylated by cellular enzymes (including guanylate kinase) to its triphosphate derivative, which is a potent inhibitor of DNA polymerase. Acyclovir triphosphate inhibits DNA synthesis by competing with doxyguanosine triphosphate for viral DNA polymerase. The DNA polymerases of HSV-I and HSV-2 utilize the triphosphate derivative as a substrate. Following incorporation of acyclovir triphosphate into the growing DNA chain, DNA synthesis is terminated. Non-phosphorylated acyclovir, the monophosphate and diphosphate derivatives do not have any significant inhibitory effect on herpes virus DNA synthesis [16,17].

In this case, patient was also given a Lemon-Mint Power Rinse Mouthwash containing Chlorine Dioxide, alcohol free, Xylitol, Zinc Acetate. Alcohol-free mouthwash is recommended because alcohol can dry the oral cavity. Zinc Acetate acts as a potential deodorizing effect on the oral cavity and can maintain moisture in the oral cavity. Xylitol acts as an antimicrobial agent that can reduce the risk of periodontal disease, dental caries, and other manifestations of hyposalivation. A stable ClO2 can help maintain a normal pH of the oral cavity. Previous studies have shown that ClO2 is an effective antimicrobial agent against many species of bacteria. Gargling with ClO2 can stimulate and increase the flow rate of saliva or replace the secretion of saliva that is lost to control the development of caries and treat infections of the mouth. ClO2 reacts with amino acids found in saliva, which are nutrients for bacteria and interfere with bacterial growth through the nutritional pathway. ClO2 can easily penetrate biofilms and increase antibacterial efficiency. ClO2 can help create an oxygen-rich environment in the oral cavity, limiting bacterial growth, especially anaerobic species. ClO2 is not only bactericidal, but has also been proven to be antifungal and anti-viral [4,6,7,8,10,15].

The clinical presentation, differential diagnosis and management of primary herpetic stomatitis are discussed. Correct diagnosis and treatment can restore well-being, avoid secondary problems for patients, and prevent the use of antibiotics or other inappropriate drugs.

REFERENCES

1. Dantas MHD, Sarmento PP, Candeia LT, Nicolau FVY, Ferreti BPR. *Acute herpetic gingivostomatitis in adult patients*. Rev Cubana Estomatol. 2018;55(4):1–6.
2. Stoopler ET, Alfaris S, Alomar D, Sollecito TP. *Recurrent Intraoral Herpes*. J Emerg Med [Internet]. 2016;51(3):324–5. Available from:http://dx.doi.org/10.1016/j.jemermed.2016.05.001
3. Anggun MPA, Rahmayanti F. *Management of Acute (Primary) Herpetic Gingivostomatitis in Immunocompetent Adult Patient*: A Case Report. Advances in Health Sciences Research. 2018;8(Idcsu 2017):30–3.
4. Kenneth M, Kaye M. *'Herpes Simplex Virus Infections.* MSD Manual Professional Version. 2020. available at: https://www.msdmanuals.com/professional/infectious-diseases/herpesviruses/herpes-simplex-virus-hsv-infections
5. George AK, Anil S. *Acute Herpetic Gingivostomatitis Associated with Herpes Simplex Virus 2: Report of a Case*. J Int Oral Heal. 2014;6(3):99–102.
6. Sumeet S, Parvathi MD, Ravindra SV, Kuber T, Dharamveer S. *Primary Herpetic Gingivostomatitis : a Case Report and Review of Literature.* TMU J Dent. 2014;1(3):119–24
7. Nugraha AP, Ernawati DS, Harijanti K, Parmadiati AE. *Psychological Stress Induced Xerostomia and Hyposalivation: The Case Study in Indonesian Female Patient.* J Int Dent Med Res. 2019;12(1):216–9.
8. Pham TAV, Nguyen NTX. *Efficacy of chlorine dioxide mouthwash in reducing oral malodor: A 2-week randomized, double-blind, crossover study.* Clin Exp Dent Res. 2018;4(5):206–15.
9. Srivenkatasatya NRM, Wang HH, Alluri S, Ciancio SG. *Phosphate buffer-stabilized 0.1% chlorine dioxide oral rinse for managing medication-related osteonecrosis of the jaw.* Am J Dent. 2017;30(6):350–2.
10. George AK, Anil S. *Acute Herpetic Gingivostomatitis Associated with Herpes Simplex Virus 2: Report of a Case',* Journal of International Oral Health, 2014; 6(3), pp. 99–102.
11. Huang CW, Hsieh CH, Lin MR, Huang YC. Clinical features of gingivostomatitis due to primary infection of herpes simplex virus in children. *BMC Infect Dis*. 2020;20(1):1-9. doi:10.1186/s12879-020-05509-2
12. Eversole LR. *Clinical Outline Of Oral Pathology: Diagnosis And Treatment (Fourth Edition)*. People's Medical Publishing House-USA , 2011:139-145.
13. Scully C, Flint SR, Bagan JV, Porter SR, Moos KF. *Oral And Maxillofacial Diseases: Fourth Edition*. Colchester, Essex CO3 3LP, UK: Informa Healthcare, 2010: 78-83.
14. Mustafa M, Illzam E, Muniandy R, Sharifah A, Nang M, Ramesh B. *Herpes simplex virus infections, Pathophysiology and Management*. *IOSR J Dent Med Sci*. 2016;15(07):85-91. doi:10.9790/0853-150738591
15. Velzen MV. *Herpes Simplex Virus Type 1 Infection: Features of Immune Surveillance and Antiviral Resistance*. Rotterdam, the Netherlands: Erasmus University Rotterdam. 2013; 10-81. Available at http://hdl.handle.net/1765/50320
16. Goldman RD. *Acyclovir for herpetic gingivostomatitis in children*. Can Fam Physician. 2016;62:403–4.
17. Sawleshwarkar S, Dwyer DE. *Antivirals for herpes simplex viruses*. *BMJ*. 2015;1(July):11-13. doi:10.1136/bmj.h3350