Review Article

Herpes Viruses: An Appraisal, Clinical Reports and Insights

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ABSTRACT

Herpes viruses occur ubiquitously among humans across the globe. This appraisal describes the molecular structure of Herpes viruses with the known types of Human Herpes Virus (Types 1-8), deconstructs, and describes the pathogenesis and clinical presentations of primary and recurrent Herpes oral infection. Illustrated here are Human Herpes Simplex Virus-1 (HHSV-1) as a primary oral herpes infection, a recurrent Herpes labialis, HHSV-1 with blood infusion, a post-op Herpes, and a radiograph of rapidly progressive periodontitis associated with Herpes. There are no strict protocols of management, and suggested treatments of oral manifestations are discussed. Therapeutic drugs available are listed and a costing for them in North America is indicated. Therapy can treat the symptoms and manifestations, but no vaccine or reliable prophylactic inoculations exists against the Human Herpes Viruses.

Key words: *Anti-virals, Gums, Infection, Herpes, Mucosa, Oral, Virus*

Herpesviridae have double stranded Deoxyribose nucleic acid (DNA) genomes, are structurally complex viruses, and evolved into eight different known types from a common pre-Cambrian Virus. The eight types are divided into three subfamilies. The eight acknowledged types of HHV's are:- Human Herpes Simplex types 1 and 2 (HHSV-1 and HHSV-2); Varicella zoster virus (VZV, HHV-3); Epstein-Barr Virus (EBV, HHV-4); Human cytomegalovirus (HCVM, HHSV- 5); Human Herpes virus 6(HHV-6); Human Herpes virus 7 (HHV-7); and Human Herpes virus 8 (HHV-8). The alpha-herpes viruses include Human Herpes Simplex Virus-1 (HHSV-1), HHSV-2 and Varicella Zoster Virus (HHV-3, VZV). These three have fast multiplication life-cycles and infect and establish themselves as latent viruses in sensory ganglia. The others are classified as Beta- and Gamma-herpesviruses and are lymphotropic.

These two groups are distinguishable from each other as well as Alpha group, on the structure of their genomes – organization and cycle of reproduction. It is not surprising that lesions fitting the description of Herpes infections are encountered in ancient texts. Historically, the virus was classically described as lip lesions dating back to the ancient Greek civilization about 2500 years ago. HHSV-1 is a double stranded DNA, in an envelope viral construct with an icosahedral capsid having a diameter of 100->110 nm. HHSV-1 is in the Alpha-herpesviridae subfamily, and the HHSV-1 follows a complicated pathogenic life-cycle. Initial HHSV-1 infection attacks epithelial cells, as a primary gingivo-stomatitis [1]. Subsequently, it assumes latency in the body of the innervating sensory neuron where later it may undergo reactivation. HHSV-1 is responsible for the primary, and the recurrent, vesicular blister infections of the lips, in the oral mucosae and the facial skin [1].

Most HHSV-2 infections occur genitally, as HHSV-I seem to provide partial immunity to HHSV-2. The prevalence of oral HHSV-2 infections may well be higher

than diagnosed clinically, because unlike HHSV-1, HHSV-2 infection rarely reactivates and consequently goes undetected. HHSV-1 and HHSV-2 may be spread by both oral routes through aerosol droplet spread and kissing, and/or via sexual intercourse or oro-genitalcontact [2-4]. HHSV-1 and HHSV-2 infection may manifest with a wide range of exhibiting stigmata, including orolabial herpes, herpetic whitlow, psychoses, herpes meningitis, pan-encephalitis, herpes gladiatorum, lesions on the skin, vulva, uterus, or penis, and eczema *herpeticum* [5-7].

AIM

This appraisal reviews the known Types of Human Herpes Virus (HHV 1-8), deconstructs and describes the pathogenesis of common Human Herpes infection (HHSV-1 and HHSV-2), illustrates oral manifestations, and indicates therapeutic drugs available with estimated costs in Canada.

PATHOGENESIS

The HHSV Type-1 and Type-2 are host-adapted, occur globally and although both cause similar lesions, they are regarded as different diseases. These two types named HHSV-1 and HHSV-2, are designated as Human alpha herpes virus Type-1 and Human alpha herpes virus Type-2 [1]. Traditionally the HHSV-1 virus is associated with orofacial diseases, specifically on the mucosal layers, whereas HHSV-2 affects the genitalia [2,3]. HHSV-1 and HHSV-2 cause respectively recurrent facial and genital herpetic lesions. Both are painful but are generally considered not to be life threatening. The three main branches deriving from the Trigeminal Nerve (Cranial Nerve-V) may produce Herpes *labials, nasalis* and *ophtalmicus,* at their terminal ends.

A Herpes infection that spreads to the brain may be potentially lethal as an infection, especially in any immuno-compromised person or newborn that has no developed immunity. HHSV-1 infection will cause necrotic destruction of the eye and may lead to blindness. From the above it is clear that each type of Herpes virus will cause a specific disease. These diseases are common but have become manifestly more prevalent among immuno-compromised people. HHSV-1 manifests in labial "cold sores", HHSV-2 triggers genital lesions, HHV-3 causes Shingles (Varicella-Zoster), HHV-4 causes Glandular Fever, Burkitts' lymphoma and naso-pharyngeal carcinoma, HHV-5 is associated with congenital abnormalities, HHV-6 causes infant *exanthema subitum* rashes, HHV-7 causes febrile illness and HHV-8 causes Kaposi's sarcoma. Besides physical examination of affected people, a cytological smear/swab test will confirm the clinical diagnosis HHV infection. The virus disrupts the DNA replication of cells which then appear as ballooning degeneration with multinucleate giant cells called Tzanck cells. Most of the initial HHSV-1 infections localizes in the oropharyngeal mucosa as primary Herpetic gingivo-stomatitis, and later as recurrent Herpes labialis [8,9].

Research shows that HHSV-1 usually settles in the Gasserian ganglion (the trigeminal ganglion), colonizes and harbors the latent virus HHSV-1 [10]. HHSV-1 also is involved in other Cranial Nerve Syndromes including: - Facial-VII Nerve (Bells' palsy), Auditory-VIII Ramsay-Hunt syndrome, Vagus-X and Glossopharyngeal-IX pathologies. HHSV-2 invades mainly the pudendal and inguinal sensory ganglia. The primary infection will occur in a susceptible immuno-deficient host (host without pre-existing effective antibodies of HHSV-1 [10,11] [**Fig 1-A&B] [Fig 2-A&B].**

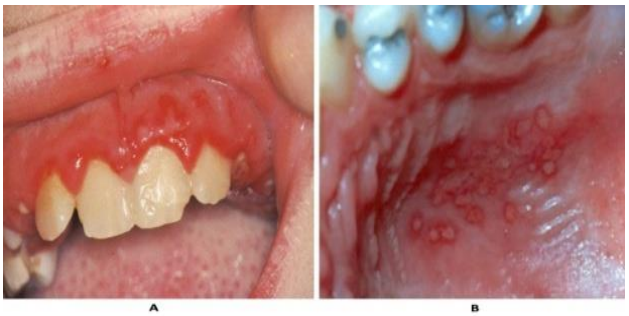

Fig 1: [A] Primary Herpetic infection of the marginal gingiva: The attached gingiva is erythematous with small ulcers are on the margins surrounding tooth #11,and #12. Small ulcers can be seen on the mucosa over the #13 and #23 locations. **[B**] **Primary Herpetic infection of the hard palate:** Rupture of vesicles leaves small **c**lusters of small circular sharply defined ulcers on the hard palate.

Recurrence of HSV-1 indicates inadequate immune antibodies to that virus [11], Recurrent infection is related to viral latency. The viral latency begins with viral entry of the HHSV-1 infecting the nerve endings and spreading into the nuclei of the sensory ganglion in place, through *centripetal* spread. Multiplication of the virus takes place in the sensory cell and neurons leading to the

cells' eventual destruction. In the majority of infected neurons, the HHSV genome persists in a dormant state for life. In many cases, the virus is reactivated and travels back to the site of portal entry through *centrifugal* neuron axonal transport [10,11] **[Fig 2 & 3]**.

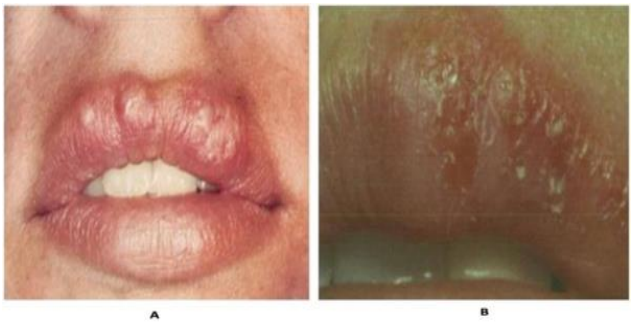

Fig 2: [A] Recurrent HHSV-1 as Herpes labialis, has an initial prodome of parasthesia or burning, followed by erythema. Vesicles form and fill with fluid in the prickle cell layer after a few hours. Vesicles often develop in clusters along the mucocutaneous junction of the lips and may extend to the adjacent skin. Although most presentations are unilateral bilateral cases do occur, and both lips and surrounding skin may be involved. [**B] Recurrent HHSV-1 as Herpes labialis:** After two to three days the vesicles rupture and crust over. Most vesicles will form a light brown crust and heal without a scar.

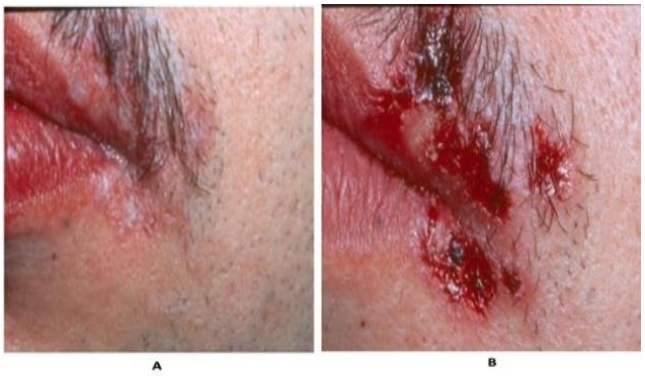

Figure 3: [A] Recurrent HHSV-1 as Herpes labialis. After the first day, vesicles form and fill with fluid and subsequently by diapedesis of blood cells. They develop crusts which may crack, ooze and bleed. [**B] Recurrent HHSV-1 as Herpes labialis.** Vesicles when filled with blood may rupture; more often vesicles form a crust and heal without a scar. The whole cycle takes up to ten days. Secondary microbial infection may induce an impetiginous lesion which sometimes leaves a scar [3].

ORAL MANIFESTATIONS

The primary lesions of infection manifest as small vesicles which can affect any part of the oral mucosa (attached and mobile mucosa). The marginal gingival, hard palate and dorsum of the tongue are favored sites. [**Figures 1-A &B]**. The gingiva becomes swollen and red, particularly in children and lymph nodes are enlarged and tender. Pyrexia may be present with malaise, and although the oral lesions will heal within a week, systemic upset may persist for weeks in both children and adults [3]. A minor trauma, such as a needle prick, or a major surgical assault, such as excision of an area of mucosa for a graft, may result in reactivation **[Figures 4A & B].**

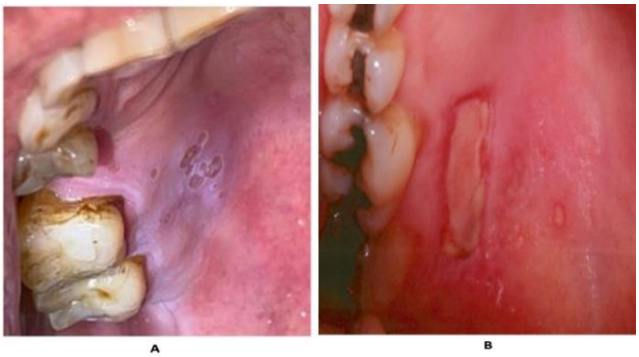

Figure 4: [A] Post-op recurrent Herpes of the palate after an injection for local analgesia. Multiple small circular ulcers on the hard palate developed three days after the injection [12]. [**B] Post-op recurrent Herpes of the palate** after an injection for local analgesia and excision of attached gingiva for a free gingival graft. The donor site is clearly demarcated as an oblong healing wound, and the ulcers outbreak is in the adjacent mucosa. A Herpes infection may moderate the immune system.

DISCUSSION

HHSV-1 and HHSV-2 may interchange and can only be differentiated and determined with serology. Precise causes for reactivation of the virus, including any systemic, or the local stimuli, remains obscure. A test for HHSV antibodies post-infection will reveal a rising titer of antibodies, which peak provides absolute but retrospective confirmation of the diagnosis. Aggressive periodontitis has been associated with high titers of anti-Herpes immunoglobulins, and for this reason, HHSV-1 has been implicated in the development of periodontal disease [13,14,15]. [**Figure 5]**

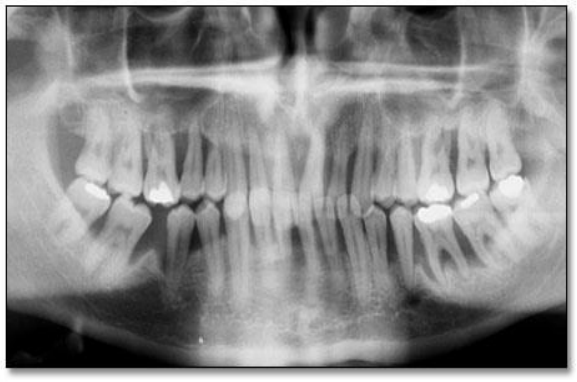

Figure 5: A Panoramic Radiograph of a 26-year-old male, with active advanced periodontitis.

His history revealed repeated labial Herpes and "gumboils". He developed severe alveolar bone loss with advanced gingival pocketing (over 7mm) around the premolar and molar teeth with furcal involvement on multi-rooted teeth. Tooth # 46 was extracted because of gum disease. Onset and progress of periodontitis has been strongly associated with dysfunctional immunity, which has been putatively focused on predisposing weakened immunity with Herpes infection, combined with poor oral hygiene and development of invasive climax microbial communities of biofilm [13-16].

Treatment of periodontitis is complex and requires specialist attention. This unfortunately may demand exodontics of unsalvageable teeth, with some form of prosthetic replacement. Early diagnosis of periodontitis includes oral hygiene intervention with tooth-scaling, root-planing, often invasive surgical interventions, and oral biome modification with anti-viral and antibiotics for therapy [19,20].

The reactivation of the Herpes virus does depend upon some stimulus of the peripheral nerve pathway and anterior nerve route, in spite of confirmed, proven established humoral- and cell-mediated immunity. Most recurrences are not predictable and may be spontaneous. There is frequently some association with emotional or physical stress, some minor or major tissue damage, a fever, exposure to the suns' ultraviolet light, and/or immune suppression [12-16]. Excluding concern over the effectiveness of the antiviral treatments, there are no strict protocols of management but there are some recommendations for mitigating treatment and management of the oro-labial and palatine herpes. Valacyclovir, Famciclovir and Acyclovir administered orally are recommended until the healing of the infection is complete. As supportive oral therapy, topical application of local analgesic paste markedly relieves pain [15]. Below is a table-list of antiviral drugs available as supportive therapy, all of which will help moderate active Herpes proliferation.

Table 1: List of antiviral medications. [15-18,26]

Medication	Dose rate	Route	Cost in Canadian Dollar
For Initial Outbreak of Oral Herpes (Primary)			
Acyclovir	400mg three times a day for 10 days	Orally	$88.90
Valacyclovir	2000 mg every twelve hours for one day	Orally	$42.69
Famciclovir	250 mg three times a day for 7 to 10 days	Orally	$60.44
For Recurrent Infection			
Acyclovir Cream 5% for recurrent herpes labialis	5 g apply 4-6 times daily for 7-10 days	Topical	$141.04
Acyclovir	400 mg three times a day for 5 days	Orally	$16.25
	800 mg twice a day for 5 days	Orally	$10.33
	800 mg three times a day for only two days	Orally	$6.20
Valacyclovir	2000mg every twelve hours for one day	Orally	$42.69
Famciclovir	1500 mg once a day	Orally	$4.53

CLINICAL MANAGEMENT

There is no ideal protocol for management of cases of Herpes infections [11]. Stress may alter a persons' metabolic state with reduced immunity, and this predisposes them to possible infections and recrudescence of latent Herpes infections. Implementation of stress

reduction strategies including adequate sleep should assist in reducing the occurrence of Herpes infections [13]. The use of anti-virals as indicated above is extensively employed but remains controversial because of unpredictable and unreliable responses. This may be due to varying immune states of infected persons. Improvements may be obvious or just minor and welcome, and consequently they are also hopefully used for prophylaxis.

Also effective is sustained oral hygiene, recommended for prevention of secondary infection. This demands regular biofilm removal, tooth brushing, flossing inter-dentally, and frequent oral lavage using saline or other antiseptic mouth washes. It is prudent and advisable to avoid physical contact with those who have active herpes infection. All facial cosmetics like lipsticks, lip-balms, skin lotions, creams ointments and all oral-hygiene paraphernalia like toothbrushes, mouth-rinses, and floss-holders, should never be communal and sharing should be strictly avoided. Exclusive personal items must be retained

THERAPEUTIC DRUGS [12,13,20-22]

Antiviral therapies: The following is the list of available antiviral medications. By introducing a DNA analogue nucleic acid (Idoxuridine), the HHSV-DNA becomes defective, cannot reproduce and its' reproduction is halted e.g. in Acyclovir cream. **[Table 1]** Hand hygiene is important. During the initial infective phase, hand washing with anti-septic soap, and/or sanitizing hands using 60% ethanol strongly assists in reducing viral spread and reduces seeding others, and infecting other parts of the face, mouth, or body [25]. Use of single-use disposable gloves, impervious transparent facial-screens and disciplined antiseptic techniques are essential for oro-dental and general health-care workers treating Herpes-infected patients. After applying topical treatments to any infected region, gloved hands should be washed immediately, and the used gloves disposed of [20,21].

CONCLUDING REMARKS

After the initial infection the virus does not remain in the affected area but survives in the nerve ganglia of the area. The Herpes-DNA is incorporated into the cell DNA and is impervious to defense mechanisms or treatment. The virus remains dormant until stimulated into re-infection. Recurrent intervals vary widely, as does the response to antiviral therapy, because the immune status of those infected varies widely, and a wide variety of underlying co-factors may have an influential aggravating effect. Trauma, extensive ultra-violet exposure from sunlight, old age, pregnancy, allergy, respiratory illnesses, menstruation, underlying systemic disease or malignancy have all been associated with recurrent HHSV-1 infection. Moderation of immunity, especially reduction, seems to allow recrudescence of the HHSV-1 virus. HIV-AIDS patients are most susceptible to HHSV-1 infection. Long-term use of anti-virals like acyclovir as a prophylaxis may induce resistant mutants with over-use [24]. Herpetic keratitis may produce corneal scarring and blindness. In neonates with underdeveloped immunity, herpetic infection may spread to the liver the lungs and brain and cause central nervous system damage and even death [10,14,25].

CONCLUSION

Herpes infections have afflicted Mankind for millennia. Herpes viruses mainly select to invade the nerves, and consequently Herpes infection frequently affects those with compromised immune systems. Although healthy immunity controls the infections, recurrence is common and serious morbidity and mortality may result. Therapy treats the symptoms and manifestations, but no vaccine or reliable prophylactic inoculations exists against the Human Herpes Viruses.

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