# Acute Herpetic Gingivostomatitis in Adults: A Review of 13 Cases, Including Diagnosis and Management

### (Gingivostomatite herpétique aiguë chez les adultes : Étude de 13 cas, incluant le diagnostic et la prise en charge)

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## Sommaire

**Objectif :** Présenter aux dentistes généralistes les signes et les symptômes caractéristiques associés à la gingivostomatite herpétique aiguë (primaire) chez les adultes et passer en revue les analyses de laboratoire et les options de traitement appropriées, ainsi que la pharmacothérapie actuelle.

**Protocole de l'étude :** Les dossiers cliniques de 13 patients adultes ont été examinés. Aucun patient n'avait d'antécédents d'infection à virus herpès simplex et tous présentaient des lésions buccales évocatrices d'une primo-infection herpétique. Les sujets étaient tous des patients d'un des chercheurs et chacun a été soumis au cytodiagnostic de Tzanck et à une culture virale.

**Résultats :** Les patients étaient âgés de 18 à 79 ans (moyenne de 37,2 ans; écart-type : 19,6) et neuf (69 %) étaient des hommes. La culture virale a été confirmée comme étalon-or pour le diagnostic. La sensibilité du cytodiagnostic de Tzanck a été de 77 % (10/13), ce qui est légèrement supérieur aux taux cités précédemment (40 % à 50 %). Dans ce groupe de patients, les patients plus jeunes (18 à 42 ans) présentaient un profil d'adénopathie fébrile, alors que les patients plus âgés souffraient essentiellement de symptômes buccaux.

**Conclusions :** La gingivostomatite herpétique primaire ne se limite pas aux enfants et peut se manifester chez des personnes de tout âge. Il est essentiel de poser un diagnostic exact et d'instaurer le traitement approprié, en particulier chez les personnes âgées et les patients immunodéprimés. Le cytodiagnostic de Tzanck peut servir de complément utile à des fins de diagnostic. Les agents antiviraux comme le valaciclovir et le famciclovir devraient être envisagés en début du traitement. Les dentistes sont souvent les premiers professionnels de la santé consultés par les patients atteints de cette affection, et il est essentiel qu'ils sachent la reconnaître.

**Mots clés MeSH :** adult; stomatitis, herpetic/diagnosis; stomatitis, herpetic/therapy

Acute (primary) herpetic gingivostomatitis (AHGS) typically affects children, but this infection also occurs in adults. Because of the limited symptoms, a dentist may be the first health care practitioner consulted. It is therefore important that dentists be able to recognize the condition (**Fig. 1**).

The causative agent for AHGS has been identified as herpes simplex virus (HSV). HSV is a double-stranded DNA virus and is a member of the human herpes virus (HHV) family officially knows as *Herpetoviridae*.[1] The virus exists in 2 forms, HSV-1 (or HHV-1) and HSV-2 (or HHV-2). Most oral, facial and ocular infections result from HSV-1, whereas HSV-2 accounts for most genital and cutaneous lower body herpetic lesions. Orogenital contact may allow either serotype to cause oral or genital lesions. The 2 forms of HSV have similar structure but differ in antigenicity, although HSV-2 is reputed to be of greater virulence. Other members of this group include varicella-zoster virus (VZV, which causes chickenpox and shingles) or HHV-3, Epstein–Barr virus (EBV) or HHV-4, *Cytomegalovirus* (CMV) or HHV-5 and 3 recent additions known simply as HHV-6, HHV-7 and HHV-8.[2]

The sites most at risk for HSV infection are the skin, eyes,
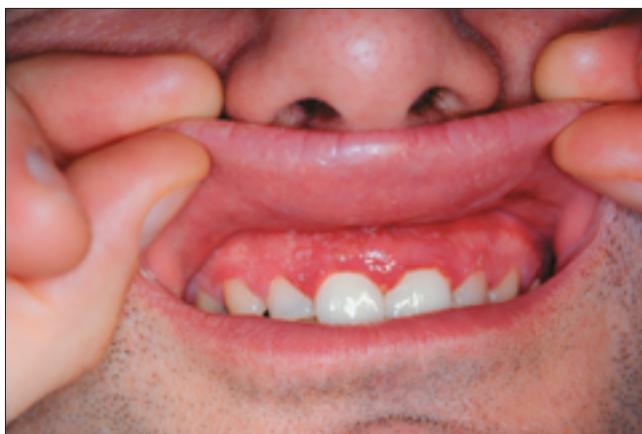
**Figure 1:** *Thirty-six-year-old man with gingival erythema, multiple small ulcers and vesicles in the attached gingiva, which are typical symptoms of acute herpetic gingivostomatitis.*



**Figure 2:** *Herpetic whitlow with vesicular skin eruption in a 21-year-old female dental student.*

mucous membranes and central nervous system. HSV is short-lived on external surfaces; infection therefore depends on intimate contact with an individual who is shedding live virus through secretions, saliva or skin.[3] In addition, the virus must come into contact with a break in the integrity of the mucosa or skin of a susceptible host. Even microscopic breaks are susceptible, so skin and mucous membranes with normal appearance may be at risk (**Fig. 2**).

The age at onset of AHGS has been reported to have 2 peaks. The main one is during childhood, usually between the ages of 6 months and 5 years, and the second peak occurs in the early 20s.[1] Most primary HSV infections in children are either asymptomatic or so mild that the child or parent does not notice. Some studies suggest only 10% to 12% of children who are infected have signs or symptoms severe enough to be remembered.[1]

The severity of signs and symptoms may be attributable to the virulence of the specific strain of HSV and the host's immune response. Once HSV penetrates the host's epithelial cells, viral replication occurs. The newly formed HSV come into contact with sensory nerve endings and are transported to the corresponding ganglion.[2] In oral labial herpes, the most common site is the trigeminal ganglion. Here the viral DNA enters the ganglion, where it becomes inactive or latent. The incubation period is the period during which viral replication and transport to the sensory ganglion occur. For HSV, this period is variable and can range from a few days to 3 weeks, but in most cases it is approximately 1 week. The severity of the primary infection depends on the degree of viral replication, the host's response to the foreign pathogen and the speed with which latency is established. Asymptomatic primary infections are thought to occur in cases in which HSV causes minimal epithelial cell destruction through replication. In these cases, the newly formed virions enter the sensory axons and become latent in the ganglion. These cases of HSV will have minimal to no manifestations. However, if these virions infect adjacent epithelial cells and continue to cause cell lysis, in conjunction with the inflammatory response mediated by

the host immune system, the primary infection is clinically evident and symptomatic.[4]

Recurrence is highly variable and can occur in response to exposure to ultraviolet light, stress, fever, cold, pregnancy or menstruation, gastrointestinal upset or local trauma.[1,2] The variability of HSV recurrence depends on previous seroconversion, general immunological status and exposure to the aforementioned situations. In terms of previous seroconversion, patients who have been exposed to another form of herpes (for example, genital, ocular or herpetic whitlow) tend to experience a milder clinical course than seronegative patients. In addition, the adult course of primary AHGS is longer and characterized by more severe symptoms than AHGS in children.

It is important to distinguish primary from recurrent herpetic infection. In general terms, a primary infection is more severe, with associated lymphadenopathy, fever and malaise. Recurrent infections occur at various intervals (ranging from monthly in some individuals to seldom in others) and affect the non-movable intraoral tissues (the hard palate and attached gingiva), in contrast to primary herpes which can occur anywhere in the mouth.[1] History may be helpful in distinguishing primary from secondary infection, as patients with a secondary infection will recall previous episodes of vesicular eruptions on their lips, thus eliminating the possibility of primary AHGS.

In this article we review a series of adult cases of AHGS to demonstrate the typical features of this viral infection. The diagnostic aids available for detection, as well as the treatment options, are also reviewed.

## Case Selection and Description of Methods

The clinical files of one of the authors (PJC) for a 5-year period (1993 to 1998) at the Montreal General Hospital were reviewed for cases suggestive of acute viral infection precipitated by HSV. We reviewed all adult cases of acute HSV infection confirmed by viral culture. A single clinician investigator (PJC) performed all Tzanck testing and viral culture.

**Figure 3:** *Gingival hyperplasia, erythema and ulceration, typical symptoms of acute herpetic gingivostomatitis, in a 30-year-old woman.*



**Figure 4:** *Twenty-four-year-old man with intact vesicles.*



**Figure 5:** *Same patient as in **Fig. 4** after preparation of Tzanck smear. Unroofed vesicles are now exposed.*

Thirteen patients were identified, 9 men and 4 women, ranging in age from 18 to 79 (mean 37.2, standard deviation 19.6) years. The patients were typically referred by their general dentist with signs and symptoms of widespread oral ulcers (tongue, gingiva and palate), gingivitis, cervical lymphadenopathy, fever and malaise (**Fig. 3**). The minimum criteria for inclusion in the review were negative history of primary or recurrent orofacial herpes, widespread bilateral oral vesicles or ulcers affecting the gingiva and mobile mucous membranes, and confirmation of the presence of HSV by viral culture.

At the time of clinical presentation, a Tzanck smear and sample for viral culture were obtained. The result of Tzanck testing was positive in 10 of the 13 cases (sensitivity 77%). The culture result was positive in all 13 cases.

## Laboratory Techniques

Although AHGS is diagnosed mainly on the basis of absence of any previous clinical history, coupled with hallmark clinical signs and symptoms, several laboratory techniques are available for detecting herpetic infections. These can be classified under 6 main headings: morphologic, immunomorphologic, serologic, virologic, immunovirologic and molecular virologic.[5]

In dentistry, the most practical techniques are either Tzanck testing (morphologic), viral culture or direct immunofluorescence (immunomorphologic). The Tzanck test is a cytological technique that involves unroofing the early viral vesicle (not the pustule or ulcer) and scraping the viral lesion gently with a tongue blade or scalpel (**Figs. 4** and **5**). The sampled material is then placed on a glass slide and stained. The presence of multinucleated epithelial giant cells is consistent with a herpes virus infection. This method generally detects only about 60% of HSV infections, although one study suggested a much lower rate of detection (40% to 50%).[5] Smears also yield no information as to whether the viral agent is HSV-1, HSV-2 or VZV. The relatively low percentage of positive results obtained with this method can be attributed to difficulty in interpreting the specimens and degree of interpreter experience, and smears taken from lesions developing later in the infection will generally be negative.[5] Nonetheless, this method is an inexpensive in-office technique and can usually confirm suspicions of AHGS.

Viral culture is considered the gold standard and the most sensitive of the diagnostic techniques. It requires the culturing of live virus, with maintenance of an environment suitable for viral growth (the viral medium), free from bacterial or fungal contamination.[5] Unsuitable conditions for transport of tissue intended for culture result in viral death and false-negative results. The test is sensitive to technique and is generally limited to the hospital setting, where equipment and facilities exist for storage and examination of the culture.

Direct immunofluorescence techniques, which require special equipment (a fluorescence microscope), are likewise restricted to the hospital setting. These methods can differentiate between the members of the herpes virus family. The technique is rapid, but considerable experience is required for interpretation. Smears are submitted fresh on special slides.

## Laboratory Findings

In this study, several interesting points came to light. The sensitivity of Tzanck testing was 77%, much higher than the 40% to 50% previously reported.[5] This high level of sensitivity may be attributable to the smears having been taken at an earlier stage in the clinical presentation. All of the patients exhibited all or most of the classic signs and symptoms of AHGS, namely fever, lymphadenopathy, malaise, gingivitis, intraoral pain and, ultimately, oral ulcerations. However, it is of note that the febrile, lymphadenopathic profile fit only the younger patients (those aged 18 to 42 years) afflicted with this condition. In contrast, the patients over 60 years of age did not have lymphadenopathy, and only one of them presented with fever. There were no peculiarities in location of vesicular eruption that could be attributed to age or sex. The most frequent sites involved were the tongue and gingiva; the palate and buccal mucosa were also affected, but not as often. Certain authors have reported that adult AHGS presents more often as a form of pharyngotonsillitis.[1] This was not our experience, and only one patient presented with symptoms suggestive of this course. However, it is difficult to draw any conclusions from this observation, as it is our suspicion that patients presenting with pharyngotonsillitis are more likely to consult a physician than a dentist. It is nonetheless important to note that AHGS may present in this manner.

In this sample more men than women were affected (9/13 or 69%). This finding contrasts with the HSV-2 results obtained by Langenberg and others [6] and Wald,[7] who found that women were more likely to acquire HSV-2 and to be symptomatic. Our results may suggest that if more women are seroconverting to HSV-2, then they will have some, though perhaps not complete, protection against HSV-1. As a result, more men will appear HSV-1 positive.

While there may indeed be a second peak in age of onset, in the early 20s, our results indicate that this infection can occur at any age: 8 (62%) of the 13 patients were over the age of 30, and the oldest was 79 years of age. It is possible that some of the cases included here as primary herpetic gingivostomatitis actually represented a severe form of recurrent intraoral herpes that had spread to affect other sites. The term acute herpetic gingivostomatitis is therefore more appropriate than primary herpetic gingivostomatitis.

## Management and Pharmacotherapy

Although adult AHGS usually runs a benign, self-limiting course in immunocompetent patients, adjunctive measures may be undertaken to minimize the severity of symptoms. Such measures are especially useful in adults, since the infection tends to run a longer, more severe course in adults than in children. Diagnosis is based on the clinical features, namely fever, malaise, cervical lymphadenopathy, marginal gingivitis, gingival hyperplasia, a negative history of herpes labialis and oral ulcerations in either the gingiva or the palate (or both). In the immunocompromised patient, prompt recognition and treatment are crucial, as these patients have a high risk for disseminated viral infection with significant morbidity.

Tzanck testing is an easy, inexpensive technique to confirm suspicion of AHGS, and it has the added advantage that it can be performed in the office. The reported sensitivity is 40% to 50%, depending on interpreter experience and degree of maturation of the viral vesicle (pustules or ulcers tend to yield lower sensitivities).

When in doubt, patients can be referred to hospital for viral culture or direct immunofluorescence, although such referral must be done soon after presentation, because of the self-limiting course of AHGS. If gingival hyperplasia is present without oral vesicles or ulcers, the workup should include routine blood testing (complete blood count with differential count and peripheral blood smear) to rule out any abnormalities suggestive of leukemia.

Conventional antiviral therapy associated with oral HSV has been acyclovir (in either cream or oral form). However, because of its poor gastrointestinal absorption and bioavailability, acyclovir has not routinely been used in the management of AHGS except for the oral suspension administered in a rinse and swallow technique.[1] Valacyclovir and famciclovir are 2 more recently developed antiviral agents that may be used in the treatment of AHGS. Valacyclovir is an altered form of acyclovir, which acts by increasing, by 3 to 5 times, the bioavailability of acyclovir (to which it is converted via hepatic metabolism).[8] It is well tolerated in healthy patients and is prescribed in doses of 1 g tid for 7 days for herpes zoster, although 1 g bid should be effective for AHGS.

Famciclovir, the oral prodrug of penciclovir, has an oral bioavailability 3 to 5 times that of acyclovir. Both penciclovir and acyclovir function through competitive inhibition of viral DNA synthesis by means of selective phosphorylation by viral thymidine kinase. Although acyclovir is a more potent inhibitor of viral DNA polymerase, the advantage of penciclovir and its analogues is that it is present in infected cells at much higher concentrations and for longer periods than acyclovir and its analogues.[9]

Penciclovir is marketed only in the United States, in a topical form (cream). However, famciclovir is available in Canada and has been successfully used by the authors of this review. The dosage of famciclovir recommended for treatment of herpes zoster is 500 mg tid po for 7 days, although 500 mg bid was effective in AHGS. A significant acceleration in clinical resolution can be seen with the use of anti-viral therapy. The earlier these medications are given, the more effective they are. They do not affect dormant virus protected in nerve ganglions and therefore will not eliminate the virus completely. After treatment of a primary infection a patient may still experience episodes of recurrent herpes labialis if the virus becomes reactivated.

The severity and quantity of intraoral lesions may significantly reduce dietary intake and predispose the patient to dehydration. Thus, it is important to balance any decrease in intake with fluids. Either nutritional supplements or a pureed or blended diet is sufficient until the patient can tolerate solids. Most systemic analgesics such as acetaminophen are adequate to manage the associated pain and malaise. A palliative mouth

rinse made by mixing attapulgite (Kaopectate, Johnson & Johnson • Merck, Guelph, Ontario) with diphenhydramine (Benadryl Elixir, Pfizer, Toronto, Ontario) (50:50 by volume) may also be helpful.

Acute forms of HSV infection pose a high risk for transmission. This potential is of particular interest to noninfected dental professionals who risk occupational exposure to oral herpes, herpetic whitlow of the digits and ocular herpes. For this reason, gloves and safety glasses must be used during the examination, especially given that the risk of asymptomatic shedding is omnipresent. Patients should also be advised to minimize intimate contact when active lesions are present, as they are at risk of spreading the virus.

## Conclusions

Primary oral herpetic infections are not limited to children but can occur at any age. The recognition of the classic presentation of signs and symptoms is important, particularly in middle-aged and elderly people, in whom the superimposition of dehydration due to AHGS can complicate pre-existing medical conditions such as diabetes mellitus and kidney disease. Likewise, acumen in the detection of AHGS, while generally of reassuring and symptomatic benefit in immunocompetent patients, can be life saving in immunocompromised or immunosuppressed patients (transplant recipients and those with human immunodeficiency virus). ❖

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