ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF ARTIFICIAL INTELLIGENCE

ISSN: 2692-515-x, Impact Factor: 9.23

American Academic publishers, volume 6, issue 01,2026

Journal: https://www.academicpublishers.org/journals/index.php/ijai

HERPETIC STOMATITIS: BIOLOGY, CLINICAL MANIFESTATIONS AND PROPHYLAXIS

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Abstract: Herpetic stomatitis is a common oral infection caused by the herpes simplex virus type 1 (HSV-1), affecting a large portion of the global population, particularly children and young adults. During primary infection in children, the disease can manifest as severe gingivostomatitis, accompanied by high fever and painful oral ulcers. For immunocompromised patients, the infection carries a risk of serious complications, including dissemination to internal organs and the central nervous system. The disease leads to severe consequences not only for health but also socio-economically. It increases medical costs, causes absenteeism from work and school, and leads to nutritional and developmental problems in children. Current treatment is aimed only at suppressing the virus and cannot completely eliminate it from the body. Furthermore, antibiotic resistance, the lack of prophylactic vaccines, and the incomplete understanding of its pathogenesis necessitate new research. This article is dedicated to analyzing the pathogenesis, clinical manifestations, and prevention methods of herpetic stomatitis based on modern scientific data. It discusses the virus's replication mechanisms, immune response, various forms and complications of the disease, as well as individual and public health preventive measures. The article aims to provide useful knowledge and recommendations for clinicians in practice, aiding in early detection, correct diagnosis, and the organization of effective prevention strategies.

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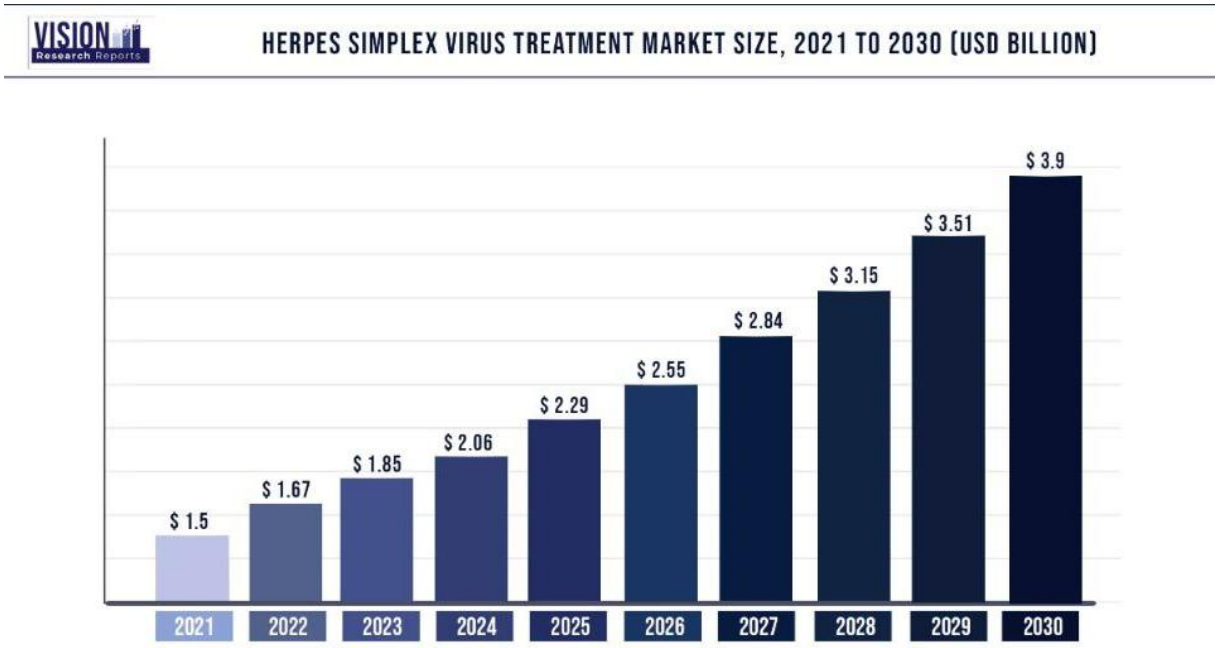
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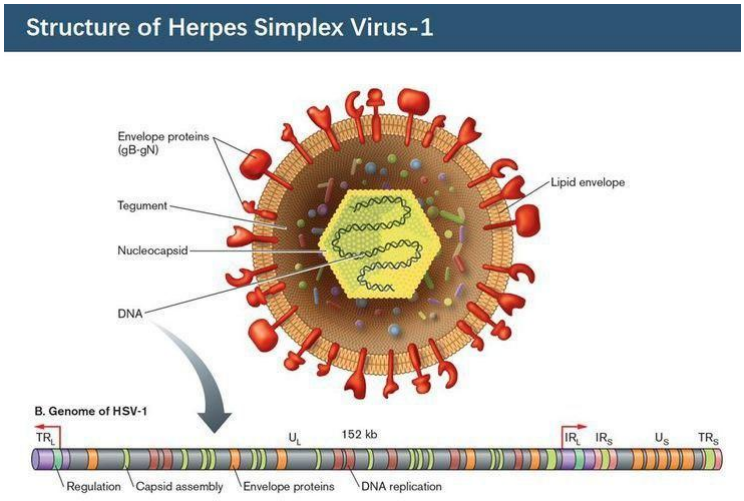
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Keywords: herpetic stomatitis; herpes simplex virus type 1 (HSV-1); pathogenesis; primary infection; recurrent herpes; herpes labialis; PCR diagnostics; antiviral therapy; acyclovir; prophylaxis; latent infection.

Introduction. Herpetic stomatitis, typically caused by the HSV-1 virus, is a highly prevalent oral infection worldwide. The World Health Organization considers it a global health concern because it can seriously affect not only the oral cavity but also the nervous system and eyes. The disease is particularly severe during primary infection in children, presenting with high fever and painful oral ulcers. In immunocompromised patients, the infection can progress, leading to dangerous complications such as liver failure or encephalitis. The socioeconomic burden of the disease is also significant. It not only results in substantial medical expenses but also adversely affects children's nutrition, growth, and school-related activities. Current treatment methods can only alleviate symptoms and cannot eliminate the virus. The rise of drug resistance, the lack of an effective vaccine, and the incomplete understanding of its



pathogenesis necessitate new research in this field. Therefore, the purpose of this article is to summarize contemporary scientific knowledge regarding the pathogenesis, clinical course, diagnosis, and prevention of herpetic stomatitis, and to develop practical recommendations for clinicians.



Main part. Herpes simplex virus type 1 (HSV-1) is one of the most widespread human pathogens, causing herpetic stomatitis in the oral cavity. The virus has a complex structure: its genome is protected by an icosahedral capsid, surrounded by

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tegument proteins located between the capsid and the lipid envelope. The outer lipid envelope contains numerous glycoproteins that play a crucial role in cell entry and evasion of the immune system. The HSV-1 genome consists of linear double-stranded DNA, which is highly compact and organized, allowing genes to overlap with one another. Gene expression occurs in a strict, sequential manner across three stages: immediate-early (α) genes, early (β) genes, and late (γ) genes. The viral replication cycle consists of the following stages:

1. Entry: The virus initially attaches temporarily to heparan sulfate on the cell surface, then binds firmly via specific receptors (e.g., nectin-1), and enters the cytoplasm through fusion with the cell membrane.

2. Delivery to the nucleus and gene expression: The nucleocapsid is transported to the nucleus. Within the nucleus, the sequential expression of viral genes begins. First, the immediate-early (α) genes are activated, followed by early (β) genes which encode enzymes necessary for viral DNA replication, and finally, the late (γ) genes that code for the structural components of new virions.

3. Assembly and release: New viral particles are assembled in the nucleus, acquire their lipid envelope, and are released from the cell. In its pathogenesis, the virus replicates extensively in the epithelial cells (keratinocytes) of the oral mucosa, leading to the destruction of these cells (cytolysis) and the formation of painful vesicles and ulcers (gingivostomatitis) in the oral cavity. Simultaneously, the virus initiates a crucial secondary pathway: it travels along sensory nerve fibers to reach neurons in the trigeminal ganglion. Here, the virus halts replication and persists in a latent state, with its DNA remaining dormant. During latency, only the regulatory LAT (Latency-Associated Transcript) RNAs are expressed. This reservoir of latent virus can later be reactivated by various triggers, leading to recurrent disease (e.g., herpes labialis).

Clinical Manifestations

Clinical Presentation of Primary and Recurrent Herpetic Stomatitis

Primary Herpetic Stomatitis (PHS), typically occurring in children during the initial infection, manifests acutely. The disease onset is characterized by severe systemic symptoms including high fever, malaise, and swollen lymph nodes. Oral manifestations progress as follows:

- Initial diffuse redness and swelling of the oral mucosa.
- Development of numerous, clustered, small, painful vesicles.
- Rapid rupture of vesicles, forming painful ulcers (aphthae) surrounded by an erythematous halo with a yellowish or grayish base.
- Ulcers can appear on any oral mucosa, including both movable (e.g., lips, cheeks) and fixed (e.g., gums, palate) surfaces.
- Significant pain often leads to difficulty in eating and drinking.

The condition is self-limiting and usually resolves without scarring within 10-14 days.

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Recurrent Herpetic Stomatitis occurs due to the reactivation of the virus that remains latent in the body following the primary infection. Systemic symptoms are typically absent or very mild. A distinctive feature of recurrence is the appearance of prodromal symptoms—such as itching, burning, or tingling—in a specific area of the mouth 1-2 days before the lesions develop.

Two common forms of recurrence exist:

- Herpes Labialis: Primarily involves the vermilion border of the lips, presenting with unilateral vesicles that subsequently crust over.
- Palatal Herpes: Located on the hard palate. Here, vesicles rupture very rapidly (within hours), forming intensely painful ulcers.



Recurrent herpes, especially the palatal form, should not be confused with recurrent aphthous stomatitis. Key differentiating features of herpes include a distinct prodromal phase beginning with itching and its frequent triggering by known factors such as stress, trauma, or sunlight.

Diagnosis. Laboratory diagnosis of herpetic stomatitis is crucial for atypical or severe forms of the disease, as well as for confirming the etiology and determining prognosis. The primary methods are aimed at detecting the virus itself or the body's immune response to it. Polymerase Chain Reaction (PCR) is based on the principle of amplifying specific segments of viral DNA and is currently considered the "gold standard." It has very high sensitivity and specificity, allowing for virus detection at any stage of the disease, even after vesicles have ruptured. Modern real-time PCR also enables the identification of the virus type (1 or 2) and its quantity (viral load), which is especially important in immunocompromised patients. Its drawbacks include high cost and the requirement for specialized laboratory conditions. Enzyme-Linked Immunosorbent Assay (ELISA) detects antibodies (IgM and IgG) against the virus in the patient's blood serum. IgM antibodies appear during acute infection, while IgG indicates past exposure to the virus and the presence of persistent immunity. This method is convenient for assessing immune status and identifying past infection but is not suitable for diagnosis in the very early days of the acute phase, as antibody development requires time. Direct Immunofluorescence (DIF) directly detects viral antigens in cells obtained from the patient (e.g., from vesicle fluid). Using specially labeled antibodies, infected cells become visible under a microscope. This method is rapid (1-2 hours) and provides accurate results, but its sensitivity may be lower compared to other methods, especially if the sample is not collected timely or is of poor quality. Each method has its specific advantages and limitations. PCR is

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preferred as the most reliable and versatile method, ELISA can be used to study the immune response, and DIF can be employed for rapid preliminary results.

Prophylaxis. The prevention of herpetic stomatitis is divided into primary (preventing initial infection) and secondary (preventing recurrences) measures.

Primary Prophylaxis (Preventing Initial Infection). Given the virus's extremely high prevalence in the population and its lifelong persistence in the body once infection occurs, the primary goal of primary prophylaxis is to interrupt transmission routes and promote safe behavioral practices. Key strategies include:

- Strict adherence to personal hygiene: Each individual should have their own personal hygiene items (toothbrush, utensils, lip balm, hairbrush). Since transmission via saliva is possible, sharing these items is strictly prohibited.
- Regular handwashing: Hands contaminated with the virus are a major vector. Washing hands with soap after touching lesions and before eating is essential. This prevents self-inoculation (e.g., to the eyes) and transmission to others.
- Limiting contact during the active phase of illness: During the period of highest transmission risk (from the appearance of prodromal symptoms until complete healing), the following should be observed:

• Avoid kissing and sharing cosmetics.

• Avoid close contact with newborns and immunocompromised individuals.

• Healthcare workers and dentists with active symptoms should be temporarily restricted from patient contact.

• Parental awareness: Adults with symptoms should avoid kissing children and tasting a child's food.

The essence of primary prophylaxis lies in widespread education about transmission mechanisms and promoting personal responsibility, as an effective vaccine is not yet available.

Secondary Prophylaxis (Preventing Recurrences). This is aimed at reducing the frequency and severity of recurrent herpes episodes, thereby improving the patient's quality of life.

1. Eliminating Trigger Factors:

• Stress management: Relaxation techniques, adequate sleep.

• Sun protection: Using high-SPF lip balms.

• Preventing trauma: Avoiding injury to the oral mucosa.

• Managing other illnesses: Timely treatment of conditions like frequent fevers or hormonal imbalances.

2. Suppressive (Prophylactic) Drug Therapy: Indicated for patients with frequent recurrences (more than 6 per year), severe episodes, or those who are immunocompromised. Administered as long-term (6-12 months) treatment. Drugs: Antiviral medications such as

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Acyclovir, Valacyclovir, and Famciclovir at low doses. Efficacy: Can reduce recurrence frequency by 70-80% and significantly decrease the level of asymptomatic viral shedding.

3. Local Barrier Methods:

• Antiviral creams (Acyclovir, Penciclovir): May somewhat alleviate the course if applied at the very first sign of prodromal symptoms.

• Hydrocolloid patches: Act as a physical barrier, protect the ulcer, reduce pain, and lower transmission risk.

4. Supporting Immunity and Micronutrients:

• L-lysine: Some studies suggest that regular intake exceeding 1000 mg per day may slightly reduce recurrences, but evidence is conflicting.

• Vitamin D: Recommended for general immune support in cases of deficiency, but a direct prophylactic effect against herpes is not conclusively proven.

• Zinc (Zinc): Topical preparations (e.g., zinc sulfate paste) may shorten healing time of lesions. Evidence for systemic prophylactic use is insufficient.

Effective prophylaxis of herpetic stomatitis requires a comprehensive approach. Primary prevention is based on hygiene and education, while secondary prevention involves lifestyle adjustments, trigger elimination, long-term suppressive therapy when necessary, and local measures.

Treatment. The treatment of herpetic stomatitis aims to suppress viral replication, shorten the duration of clinical symptoms, alleviate pain and other manifestations, and prevent complications. The treatment strategy is determined based on the type of infection (primary or recurrent), its severity, and the patient's immune status. It is important to understand that treatment controls the virus but cannot completely eliminate it from the body. The main treatment method is antiviral (etiotropic) therapy. For this purpose, drugs from the acyclic nucleoside group are used, which selectively block the synthesis of viral DNA. Systemic therapy (orally administered tablets) is the primary method for primary, severe, or frequently recurring infections, as well as for immunocompromised patients. This involves the use of drugs such as acyclovir, valacyclovir, and famciclovir. Primary herpetic stomatitis is typically treated for 5-7 days with, for example, acyclovir (200 mg five times daily) or valacyclovir (500 mg twice daily). For episodic treatment of recurrent infection, a short course with a high dose is effective if started within the first 24-48 hours of symptom onset (e.g., valacyclovir 2000 mg twice daily for 1 day). For patients with

TABLE 1. Treatment Options for Herpes Simplex Virus-1[20, 27]

Drug	Dosage
Episodic Oral Treatment	
Acyclovir	200 mg 5x/day or 400 mg 3x/day
Famciclovir	1,500 mg once for 1 day
Valacyclovir	2 g twice for 1 day
Episodic Topical Treatment	
Acyclovir cream	Apply 5x/day for 4 days
Docosanol cream	Apply 5x per day until healed
Penciclovir cream	Apply every 2 hours while awake for 4 days
Treatment to Prevent Recurrences	
Acyclovir	400 mg twice per day (ongoing)
Valacyclovir	500 mg once per day (ongoing)
Sunscreen	SPF 15 or higher

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frequent recurrences (more than 6 per year), suppressive therapy is recommended—long-term (for months) administration of antiviral drugs at low doses, which significantly reduces the frequency of recurrences. Topical antiviral agents (creams based on acyclovir or penciclovir) may only play an auxiliary role in mild labial herpes; they might shorten the course slightly, but their effectiveness is significantly lower compared to systemic therapy.

Symptomatic and supportive therapy is aimed at alleviating the patient's condition. This includes antiseptic rinses (e.g., chlorhexidine, lidocaine solution) to cleanse the oral cavity and reduce local pain; paracetamol or ibuprofen for fever and pain; and maintaining fluid and electrolyte balance (rehydration). Food should be chosen to be mild, cool, easily digestible, and non-irritating to the mucosa. Treatment protocols change in specific clinical situations. Patients with severe immunodeficiency (HIV infection, transplant recipients, cancer) often require high-dose and prolonged antiviral courses; in cases of acyclovir resistance, alternative drugs such as foscarnet or cidofovir are used. Herpes infection in newborns is considered life-threatening and requires immediate initiation of intravenous acyclovir. Herpetic keratitis (eye involvement) or encephalitis (brain involvement) demands urgent specialized medical care and high-dose intravenous antiviral therapy. Modern treatment is highly effective. The key to success is starting systemic antiviral therapy as early as possible and adopting an individualized approach tailored to each patient's needs—episodic therapy for infrequent recurrences, suppressive therapy for frequent recurrences, with special attention to symptomatic support in children and severe cases.

Conclusion. Based on contemporary understanding of herpetic stomatitis caused by the Herpes Simplex Virus Type 1 (HSV-1), the following key conclusions can be drawn: This disease is not merely a local oral cavity problem but a systemic and chronic infection characterized by neurotropism. Its most crucial defining aspect is the inability to completely eliminate the virus from the body, while simultaneously having the capability to control it with high efficacy. The disease's foundation lies in HSV-1's ability to establish a lifelong latent (hidden) state within sensory neurons. Following the initial infection, the virus resides in the ganglia and can reactivate under the influence of triggers such as stress, sunlight, or decreased immunity, leading to clinical symptoms. Clinical manifestations differ sharply depending on the patient's immune status. Primary herpetic stomatitis occurs mainly in children, presenting with severe systemic symptoms (fever, malaise) and widespread painful vesicles and ulcers on the oral mucosa. The recurrent form is localized, begins with prodromal symptoms like itching or burning before lesions appear, and typically manifests on the lips or palate. Diagnosis, especially in recurrences, is usually based on distinct clinical presentation. In doubtful, atypical, or severe cases, Polymerase Chain Reaction (PCR) is considered the "gold standard," detecting viral DNA with high accuracy. Enzyme-Linked Immunosorbent Assay (ELISA) can be used to assess immune status, and Direct Immunofluorescence (DIF) can provide a rapid preliminary result. While treatment cannot eradicate the virus, it enables effective control. Systemic antiviral therapy (acyclovir, valacyclovir, famciclovir) is the primary method for severe primary forms and immunocompromised patients. For recurrent infections, episodic therapy (treating individual outbreaks) or suppressive (prophylactic) therapy (to prevent frequent recurrences) is applied. Local and symptomatic treatments play a supportive role. Prophylaxis requires a two-tiered approach: primary prophylaxis prevents transmission (hygiene, limiting contact), while secondary prophylaxis prevents recurrences (managing trigger factors, prophylactic drug therapy). In summary, the successful management of HSV-1 stomatitis is based on accurate diagnosis, the selection of an individualized treatment strategy, and comprehensive patient

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education. Future research should be directed towards eliminating the latent virus and refining individualized management protocols.

Disclaimer: This article is a review article based on an analysis of the existing scientific literature on the herpes simplex virus. This material is provided solely for informational and educational purposes, and clinical decisions should not be based on it. The diagnosis and treatment of patients should be based on relevant clinical guidelines (e.g., WHO, U.S. Department of Health) and the individual assessment of licensed physicians. The author(s) are not responsible for any adverse consequences resulting from the application of the information contained in this article.

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