

# Oral herpes simplex virus infection in patients undergoing chemotherapy – an integrative review

## Orale Herpes-simplex-Virus-Infektion bei Patienten unter Chemotherapie – eine integrative Überprüfung

### Abstract

**Aim:** The purpose of this study is to undertake an integrative literature review in order to determine the prevalence, etiology, and reactivation of oral HSV infection in patients receiving chemotherapy (CT).

**Methods:** The study was carried out in the PubMed/MEDLINE, Embase, Virtual Health Library, and Scopus databases, using the descriptors “Herpes Simplex”, “Viral Diseases”, “Mouth”, and “Antineoplastic Agents”.

**Results:** The findings suggest that HSV infection is widespread in this group of patients and can be severe. HSV infection is frequent in CT patients, and treatment should begin as soon as it is feasible, utilizing antivirals to avoid future difficulties, as patients are immunocompromised.

**Conclusion:** It is critical for health professionals to be fully informed on the dangers and treatment choices available, with the most appropriate therapy for each circumstance. Furthermore, more recent research with acceptable methodological rigor is required to better quantify the prevalence of HSV in these patients.

**Keywords:** Herpes simplex, virus diseases, mouth, antineoplastic agents

### Zusammenfassung

**Zielsetzung:** Um die Prävalenz, Ätiologie und Reaktivierung von oralen HSV-Infektionen bei Patienten, die eine Chemotherapie (CT) erhalten, zu bestimmen, wurde eine integrative Literaturanalyse durchgeführt.

**Methode:** Die Studie wurde in den Datenbanken PubMed/MEDLINE, Embase, Virtual Health Library und Scopus unter Verwendung der Deskriptoren „Herpes simplex“, „Viruskrankheiten“, „Mund“ und „Antineoplastische Mittel“ durchgeführt.

**Ergebnisse:** Die Ergebnisse weisen darauf hin, dass eine HSV-Infektion in dieser Patientengruppe weit verbreitet ist und schwerwiegend sein kann. HSV-Infektionen sind bei CT-Patienten häufig, und die Behandlung sollte so rasch wie möglich mit antiviralen Mitteln begonnen werden, um künftige Schwierigkeiten zu vermeiden, da die Patienten immungeschwächt sind.

**Schlussfolgerung:** Es ist von entscheidender Bedeutung, dass die Angehörigen der Gesundheitsberufe umfassend über die Gefahren und die verfügbaren Behandlungsmöglichkeiten informiert sind und die für die jeweilige Situation am besten geeignete Therapie kennen. Darüber hinaus sind neuere Untersuchungen mit akzeptabler methodischer Strenge erforderlich, um die Prävalenz von HSV bei diesen Patienten besser zu quantifizieren.

**Schlüsselwörter:** Herpes simplex, Viruskrankheiten, Mund, antineoplastische Mittel

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## Introduction

Herpes simplex virus (HSV) infections are comorbidities with global prevalence. In 2016, it was estimated that approximately 66% of the population (0–49 years of age) worldwide had HSV type 1 (HSV-1) infection in some region of the body and 13.2% (15–49 years of age) lived with HSV type 2 (HSV-2) as latent carriage [1]. HSV-1 is highly related to oral herpes simplex, commonly producing the classic symptoms of mucocutaneous vesicles that coalesce and rupture, with primarily mouth-to-mouth transmission, as opposed to HSV-2 which is more associated with genital infections [1], [2].

Regardless of viral typing, HSV infection pathogenesis characteristically affects skin and mucosa regions, resulting in replication in epithelial cells of the main site of infection [1]. Subsequently, it affects sensory nerve ganglia, promoting the latent phase of infection, characterized by viral replication in its dormant state, a stage responsible for producing the clinical manifestation of reappearances after the first infection [1], [2], [3]. Several stimuli are responsible for promoting HSV reactivation, such as physical and emotional stress, sleep deprivation, fever, and exposure to ultraviolet rays, hormonal imbalance, and immunosuppression of different origins [4].

Patients undergoing chemotherapy (CT), a treatment for different types of cancer, suffer many side effects, which vary depending on the affected organ, tumor stage, CT drug combination, and dosage. One of the side effects of the medications is immunosuppression, which is a key role in HSV reactivation, making such patients more likely to develop the disease with increased severity and comorbidity [5].

The aim of this study was to conduct an integrative review of the literature, focusing on the prevalence of HSV episodes in patients undergoing CT, promoting a better understanding of the possible relationship between CT immunosuppression and HSV infection in individuals undergoing CT without head and neck radiotherapy, and enabling better predictability and specific care for herpes simplex episodes in the oral cavity.

## Methods

The integrative literature review was performed according to Page et al. [6] and included the following steps: subject identification, literature search, study selection based on pre-established inclusion criteria, data analysis and compilation, and presentation of outcomes.

The guiding question of the review was “What is the prevalence of HSV infection in cancer patients treated by chemotherapy?” based on the PECO strategy (P: cancer patients; E: undergoing chemotherapy; C: comparator (not applicable in this study); O: HSV infection).

The search was conducted in the following databases: PubMed/MEDLINE, Embase (via Elsevier), Biblioteca Virtual em Saúde (BVS) and Scopus. The descriptors “Herpes simplex”, “virus diseases”, “mouth” and “antineoplastic

agents” were used, as well as their correlated terms, using the Boolean operators “AND” and “OR”. Studies were included if they were available in full and addressed the topic in question, with no language or publication period restrictions. Studies were excluded if they were review articles, theses, dissertations, editorials, case reports, case series, or involved patients undergoing head and neck radiotherapy.

After searching all databases, the retrieved records were transferred to the EndNote Web® reference manager (Clarivate, London, UK) to identify duplicates. Two independent reviewers (A.R.C. and R.L.S.) read the titles and abstracts of each article and excluded studies that did not meet the eligibility criteria. Following this pre-selection, full-text reading was performed to analyze which studies exactly met the established criteria. Any discrepancies were resolved through discussion with a third reviewer (P.S.S.S.).

The study data were extracted by two researchers (A.R.C. and R.L.S.), and the studies selected for inclusion were extracted using a standardized table including the following information: authors/year/country of origin, type of study, population, sex, age, objective, methodology, conclusion (Table 1).

To tabulate the data, a database comprising the obtained information was employed and structured in a Microsoft® Excel® spreadsheet for Microsoft 365 MSO (version 2301; Microsoft Corporation, Redmond, WA, USA). The information in the selected papers was gathered using a descriptive analysis.

## Results

By searching the different databases and crossing the descriptors, 280 articles were found; 85 in PubMed, 10 in Scopus, 115 in VHL, and 70 in Embase. A total of 66 duplicate articles were removed. The titles and abstracts of 214 articles were then read, after which 18 articles were selected to be read in full. At the end, according to the inclusion and exclusion criteria, 11 articles were selected to compose this review (Figure 1)

The findings of this study reflect a wide age range of the individuals studied, ranging from young children aged 6 months to adults aged 84 years. In total, 2,225 patients were analyzed in the 11 papers that comprised this evaluation (Table 1).

In addition to viral infections, bacterial and fungal infections with the presence of one or more agents were found. In one of the studies, a higher percentage of HSV-associated lesions was observed in patients concomitantly undergoing CT and bone-marrow transplant, especially autologous transplants [7]. Bergmann et al. [8] observed most HSV-associated ulcerated lesions in the alveolar process of patients undergoing CT. Another study reported high prevalence of HSV-1 in children with CT-induced oral mucositis [9]. However, there is disagreement regarding the association of HSV-1 with mucositis severity or age. While some studies state that there is no relationship,

**Table 1: General characteristics of the articles included in this study**

Authors/year/ country of origin	Type of study	Population/ sex/age	Objective	Method	Results	Conclusion
Dreizen, et al. 1982/ USA	Retrospective observational	1,000 individuals/ 634 males and 456 females/17 to 82 years old	Identify the prevalence of oral infections among adult hospitalized patients with acute leukemia, chronic leukemia in the blastic phase, and chronic myelocytic leukemia in the blastic phase.	A healthcare service's 15- year archives of care were reviewed.	Oral infection in 32.9%, of which 51.8% were fungal, 33.1% were bacterial, 15.1% were viral (HSV). Infection with one organism occurred in 80.9% of infected patients, and 19.1% were infected with two to five organisms.	Every third adult patient hospitalized for acute leukemia gets an oral infection related to medication use. Each oral infection in these people represents a risk to their well-being and survival.
Montgomery et al./1986/ USA	Cross sectional	29 individuals/ not reported/ not reported	To ascertain the proportion of intraoral soft tissue lesions caused by HSV in patients receiving chemotherapy (CT) as antineoplastic treatment.	Patients with intraoral and/or adjacent soft tissue lesions were examined, 14 received conventional CT and 15 with CT followed by bone marrow transplantation (BMT). All lesions were cultured for HSV virus.	This study analyzed 29 lesions and found that 48% of them tested positive for HSV.	The incidence rate of 48% for intraoral soft tissue lesions attributable to HSV in an unknown mix of seronegative and seropositive patients is consistent with data reported in the medical literature.
Barret, et al./ 1987/ Australia	Prospective clinical	44 individuals/ not reported/ not reported	To determine the range and incidence of oral complications that occurred in a group of patients undergoing intensive conventional CT for acute leukemia.	Diverse culture methods detected fungi, viruses, and bacteria, with cytopathological analysis. Patients received oral care with sodium bicarbonate mouthwash and topical nystatin/amphotericin. No chemical anti-plaque agents were used.	Oral complications were detected in 89% of hospital admissions for the treatment of acute leukemia in adults. Hemorrhagic phenomena (77%), neutropenic ulcers (49%), and HSV infections (39%) were the most common.	Oral issues are frequent in patients undergoing intense CT for acute leukemia remission. Monitoring daily oral changes aids early intervention in problems and indicates systemic factors.
Beattie et al./ 1989/ Scotland	Experimental	28 individuals/ not informed/ not informed	To assess whether a relationship exists between the presence of HSV and the development of oral ulcers in cancer patients undergoing CT.	Patients with neutropenia and oral ulcers were examined. Swabs were collected for viral isolation and mycological culture. Suspected cultures were further examined using monoclonal antibodies against HSV.	In 29%, yeast was cultured in the absence of any viral growth; however, in four cases, two of which had solid tumors, HSV (type I) was cultured in the absence of fungal infection. HSV and <i>C. albicans</i> were isolated in nine patients.	HSV may have a significant influence on the development of oral ulcers in many patients, along with the presence of <i>C. albicans</i> .

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**Table 1: General characteristics of the articles included in this study**

Authors/year/ country of origin	Type of study	Population/ sex/age	Objective	Method	Results	Conclusion
Bergmann, Mogensen, Ellegaard/ 1990/ Denmark	Prospective cohort	46 individuals/ 26 females and 20 males/ 39 to 69 years old	Describe the location of intraoral ulcers; describe the non-viral microbial flora in patients with and without oral ulcers; investigate the potential relationship between intraoral ulcers and neutropenia.	Patients with or without ulcers were compared regarding the underlying disease, presence of teeth, qualitative composition of the oral microflora, HSV positivity, history of cold sores, leukocyte and platelet counts, and duration of fever.	Viral saliva cultures revealed an association between the presence of HSV in saliva and the presence of intraoral ulcers. Viral cultures of the ulcers showed growth of HSV in 11 (61%) of the 18 patients with ulcers. HSV-positive ulcers were more frequently located in the alveolar process.	Intraoral ulcers are associated with HSV-1 infection and in some cases are likely caused by the virus, particularly when located in the alveolar process.
Bergmann et al./1995/ Denmark	Randomized , double- blind, placebo- controlled	74 individuals/ 41 females and 33 males/ – acyclovir group, 18 to 84 years old – placebo group, 18 to 78 years old	Evaluate the prophylactic effect of the antiviral medication acyclovir on oral ulcers in patients with acute myeloid leukemia (AML) receiving remission-inducing CT, and assess the role of the HSV virus in the etiology of these ulcers.	The study involved 74 HSV- seropositive patients: 37 took oral acyclovir (800 mg daily), and 37 received a placebo. Daily examinations were conducted over 28 days.	Acyclovir resulted in fewer oral infections than placebo. This reduction involved herpes labialis, intraoral ulcers excluding soft palate, and acute necrotizing ulcerative gingivitis. Soft palate ulcers were similar. HSV type 1 in saliva decreased from 15 (placebo) to one case (acyclovir).	The findings suggest that acute necrotizing ulcerative gingivitis may also be caused by HSV. Prophylaxis with acyclovir should be considered for patients with acute myeloid leukemia during remission-inducing therapy.
Anirudhan et al./2007/ India	Experimental	70 individuals/not reported/ 6 months to 15 years old	Comprehend the causes of oral mucosal inflammation and determine if it can trigger health issues in other parts of the body.	The study tracked children under 15 with leukemia, undergoing CT, who experienced mucositis. Researchers collected data on CT details, neutropenia duration/severity, antibiotic/steroid use, oral mucositis extent, and tested for fungi, bacteria, and HSV.	There were 100 episodes of mucositis. The majority occurred during the CT induction phase, and ulcers were the most common presentation. Neutropenia was found in 64% of the episodes, and 39 fungal organisms were isolated from the oral cavity. Patients showed elevated antibody titers against HSV, but in only one case was the virus isolated in culture.	Herpes serology is useful for predicting the occurrence of recurrent oral lesions caused by HSV in patients undergoing CT. HSV-1 isolation in culture occurred in only 1% of the episodes, whereas the Tzanck technique could have identified more cases of HSV.



(Continued)

Table 1: General characteristics of the articles included in this study

Authors/year/ country of origin	Type of study	Population/ sex/age	Objective	Method	Results	Conclusion
Ramphal, et al./2007/ Canada	Prospective cohort	75 individuals/46 males and 29 females/ average of 6.2 years	To determine the prevalence of oral HSV in pediatric oncology patients with febrile neutropenia and to describe the association between oral HSV and prolonged fever, neutropenia, mucositis, and response to initial antimicrobial therapy.	Buccal swabs and blood samples were collected from oncology patients experiencing febrile neutropenia, and they were tested for HSV.	Out of the 75 samples of oral swabs and blood samples obtained, only 7 oral swab samples (9%) and 2 blood samples (3%) tested positive for HSV. Oral HSV was not associated with prolonged fever or neutropenia. Oral HSV was linked to a less successful response to initial antimicrobial therapy.	The prevalence of HSV infection in pediatric oncology patients with febrile neutropenia is low, and the presence of oral HSV is not associated with prolonged fever. The presence of oral HSV is linked to prolonged mucositis and a poorer response to initial antibiotic therapy.
Djuric et al./ 2009/ Serbia	Longitudinal	60 individuals/ 30 females and 30 males/ 19 to 79 years old	To assess the prevalence of HSV reactivation using different techniques and evaluate its potential role in causing oral mucosal damage in cancer patients undergoing CT.	A clinical examination and complementary tests were conducted at two different time points: prior to the initiation of CT and after 14 days.	PCR revealed viral DNA in 71.7% pre-CT and 85.0% post- CT. Viral culture showed 33.3% and 40.0% positivity pre- and post-CT, resp., while direct immunofluorescence showed 3.3% and 11.7%, resp. No major HSV-1 reactivation change was observed post-CT, including in patients with mucositis.	Reactivation occurs independently of antineoplastic CT. Considering the fact that HSV was found in patients both with and without mucositis, the role of HSV in causing damage to the oral mucosa in cancer patients undergoing CT remains uncertain.
Rodriguez et. al./ 2010/ Chile	Retrospectiv e	148 individuals/ 91 males and 57 females/ average of 6.7 years	Compare the prevalence of oral mucosa pathologies in children with cancer who were hospitalized and treated with CT in the years 1997 and 2007.	Data from patients with neoplastic conditions undergoing CT were evaluated, recording their general information and oral pathologies.	A significant decrease in the number of patients with oral pathologies was found in 2007 compared to 1997. Herpetic lesions were observed in 14.8% of patients in both years.	It is necessary to continue studying measures to prevent, diagnose, and/or treat oral pathologies early in patients undergoing antineoplastic treatment.
Aggarwal et al./ 2014/ India	Experimental	62 individuals (32 cases and 30 controls)/ not reported/ 6.3±3.4 years old	To investigate the detection of HSV-1/2 in oral mucosal lesions of children undergoing CT using serology (ELISA) and conventional and real-time PCR.	To assess prevalence of oral manifestations in pediatric patients with ALL during CT and evaluate independent risk factors.	The ELISA test for IgG and IgM antibodies to HSV-1/2 was positive in 34% of the cases and 30% of the controls, while qualitative PCR for HSV-1 was positive in 25% of the cases and none of the controls. Quantitative PCR detected HSV-1 in 66% of the cases and HSV-2 in 69% of the cases.	HSV-1 is common in children with CT-induced oral mucositis, regardless of age or the severity of the condition. Real-time quantitative PCR may be more sensitive in detecting the virus in tissue samples.

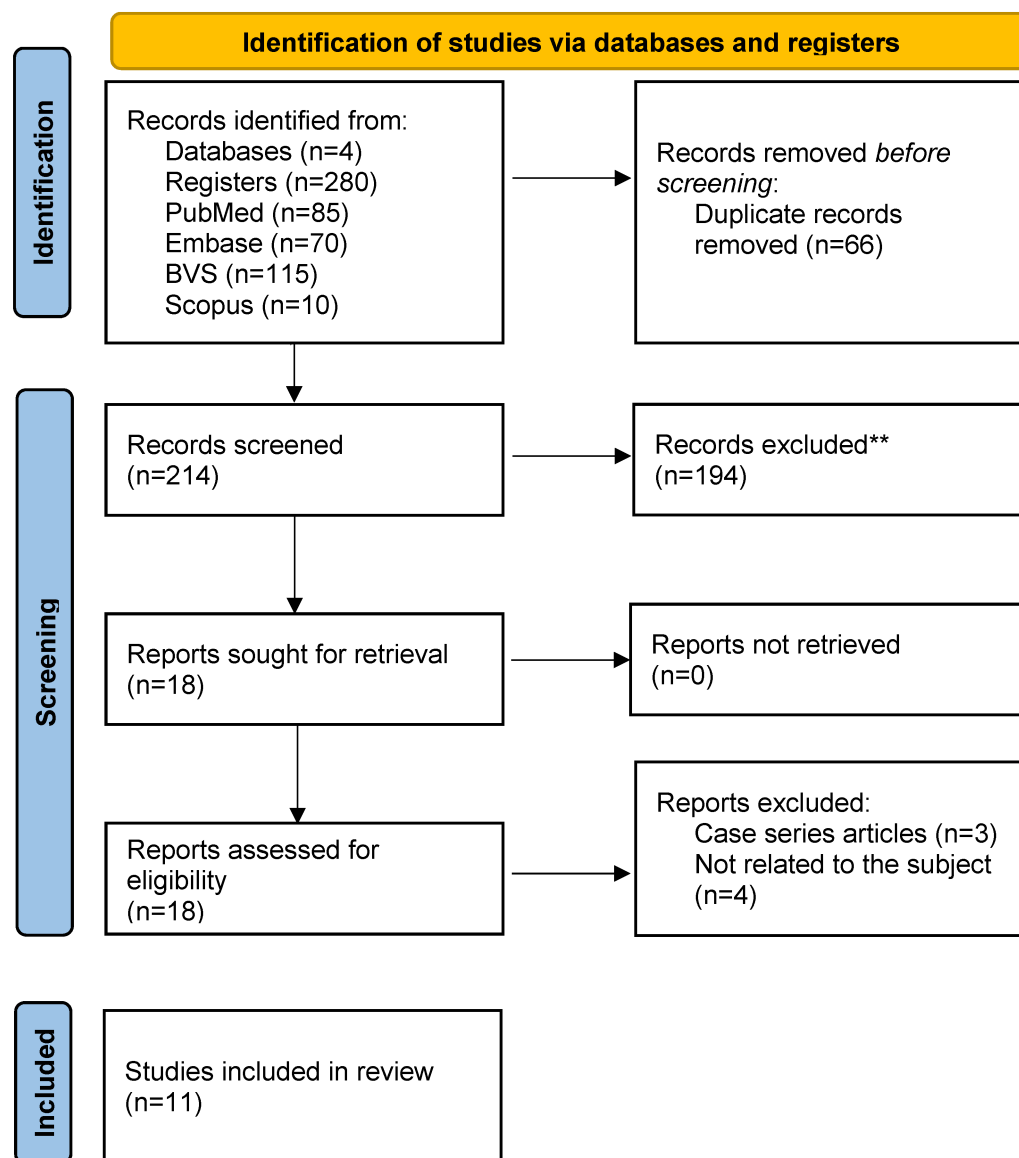


Figure 1: Description of the article search for this integrative review

others suggest that oral HSV is associated with prolonged mucositis and worse response to initial antibiotic treatment [10]. Although some studies found the classic form of herpes labialis, in most cases, ulcers were seen with association with HSV. Besides oral HSV, other oral manifestations were found in cancer patients undergoing CT, such as gingivitis, caries, mucositis, periodontitis, cheilitis, primary herpetic gingivostomatitis, dry lips, mucosal pallor, mucosal petechiae, and ecchymoses.

Several laboratory techniques were utilized to detect HSV in the studies reviewed here, including polymerase chain reaction (PCR), serology, immunoenzymatic assay, and immunofluorescence from cell culture, swab and blood tests. Aggarwal et al. [9] used PCR (qualitative and quantitative) and ELISA (IgG and IgM) tests and observed that real-time quantitative PCR may be more sensitive in detecting HSV-1 in tissue samples. In 2007, Anirudhan et al. [11] attributed the low incidence of HSV-1 detection to the technique used for laboratory diagnosis (culture and serology), and states that the Tzanck technique could

have identified more cases of HSV. This test is performed by scraping the base and sides of a vesicle with a scalpel; the material thus obtained is then stained with Wright's or Giemsa's stain, which visualizes specific characteristics of HSV such as multinucleated giant cells. These are a sign of infection with herpes simplex or shingles [12]. A decrease in cases of oral mucositis and candidiasis was observed between the years 1997 and 2007, but the incidence of HSV cases remained the same. Furthermore, it was concluded that the development of prophylactic protocols is necessary to prevent patients undergoing CT from developing oral lesions [13]. In another study, a comparison was made between groups of HSV-seropositive patients, where one group received prophylactic acyclovir and the other group received placebo. A statistically significant reduction in the incidence of labial herpes was found in the group receiving acyclovir prophylaxis compared to the group receiving placebo [8]. Only one study has reported the treatment used when herpes

simplex occurs in cancer patients undergoing CT, using intravenous acyclovir [7].

## Discussion

In the current review, the studies pointed out an association between infections by different microorganisms, highlighting the importance of adequate monitoring of oral health during CT treatment. We observed that the use of a prophylaxis protocol in oncology patients seropositive for HSV-1 undergoing CT may be well indicated, considering the incidence of cases of reactivation due to immunosuppression caused by CT. Moreover, divergent diagnostic laboratory results were observed according to the technique used, showing a need to increase the knowledge of health professionals and employ techniques best suited to these cases, to ensure the most efficacious treatment of lesions.

## Conclusions

There are few studies in the literature that address the prevalence of HSV infection in patients undergoing CT, despite the fact that they are immunocompromised patients who are susceptible to opportunistic infections (either new or reactivations). HSV is the pathogen most commonly associated with viral infections in immunocompromised patients undergoing CT. More studies with better methodological rigor as well as more current investigations are needed to measure the prevalence of HSV infection in oncology patients undergoing CT.

## Limitations

The limitations of the study are that the studies addressing herpes in patients undergoing CT are not standardized. For instance, viral detection methods and information on episodes of herpes simplex prior to CT vary from study to study, thus preventing comparability. In addition, only one study included the treatment regimen used against HSV, and even then, it did not specify doses used, only the mode of administration. A small number of studies have reported the characteristics of the clinical manifestations of oral herpes simplex in the group of patients under CT.

## Notes

### Competing interests

The authors declare that they have no competing interests.

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