**UNIVERSIDADE FEDERAL DE PERNAMBUCO**

**CENTRO DE CIÊNCIAS DA SAÚDE**

**PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA**

**DOUTORADO EM ODONTOLOGIA**

**ANDREZA BARKOKEBAS SANTOS DE FARIA**

# ESTUDOS RELACIONADOS À MUCOSITE ORAL E SUA REPERCUSSÃO EM PACIENTES JOVENS COM CÂNCER

Recife, 2014

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Tese apresentada ao Colegiado do Programa de Pós-Graduação em Odontologia com área de concentração em Clínica Integrada do Centro de Ciências da Saúde da Universidade Federal de Pernambuco, como requisito para obtenção do grau de Doutor em Odontologia

Orientador: Prof. Jair Carneiro Leão, PhD

Recife, 2014

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**ATA DA DÉCIMA SEXTA DEFESA DE TESE DE DOUTORADO DO PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA DO CENTRO DE CIÊNCIAS DA SAUDE DA UNIVERSIDADE FEDERAL DE PERNAMBUCO.**

Às quatorze horas do dia 26 do mês de fevereiro do ano de dois mil e quatorze, reuniram-se em caráter de Solenidade Pública, a Comissão Examinadora para avaliar o Trabalho da Doutoranda **ANDREZA BARKOKEBAS SANTOS DE FARIA** , candidata ao Grau de Doutor em Odontologia com área de concentração em Clínica Integrada, os membros da Banca Examinadora, composta pelos professores: Profa.Dra. ALESSANDRA DE ALBUQUERQUE TAVARES CARVALHO, Universidade Federal de Pernambuco, atuando como Presidente, Profa.Dra. SANDRA CONCEIÇÃO MARIA VIEIRA, da Universidade de Pernambuco, como primeiro examinador, Prof. Dr. EMANUEL SÁVIO DE SOUZA ANDRADE, da Universidade de Pernambuco, como segundo examinador, Profª Drª LUCIA CARNEIRO DE SOUZA BEATRICE, da Universidade Federal de Pernambuco como terceiro examinador, Prof. Dr. LUIZ ALCINO MONTEIRO GUEIROS, da Universidade Federal de Pernambuco como quarto examinador, A sessão foi aberta pela Profa.Dra. ALESSANDRA DE ALBUQUERQUE TAVARES CARVALHO, Vice - Coordenadora do Programa de Pós- Graduação em Odontologia, fez as apresentações e compôs a Banca Examinadora, que agradeceu a presença de todos. Iniciando convidou a Doutoranda ANDREZA BARKOKEBAS SANTOS DE FARIA , sob a orientação do Prof. Dr. JAIR CARNEIRO LEÃO, para iniciar sua apresentação, sendo comunicado que conforme consta das normas a candidata teria trinta minutos para exposição. A doutoranda iniciou a apresentação do seu trabalho intitulado: **"ESTUDOS RELACIONADOS À MUCOSITE ORAL E SUA REPERCUSSÃO EM PACIENTES COM CÂNCER"**. Concluída a apresentação, a Banca Examinadora compôs a mesa e foi dado inicio a arguição. Após o término das arguições os examinadores reuniram-se em secreto para deliberações formais. Ao término da discussão, atribuíram a candidata os seguintes conceitos: Profa. Dra. SANDRA CONCEIÇÃO MARIA VIEIRA, (APROVADA), Prof.Dr. EMANUEL SÁVIO DE SOUZA ANDRADE, (APROVADA), Profa. Dra. LÚCIA CARNEIRO DE SOUZA BEATRICE , (APROVADA), Prof. Dr. LUIZ ALCINO MONTEIRO GUEIROS (APROVADA), Profa. Dra.ALESSANDRA DE ALBUQUERQUE TAVARES CARVALHO , (APROVADA), a candidata recebeu por unanimidade o conceito (APROVADA) é considerada (APROVADA), devendo a mesmo acatar as sugestões da Banca Examinadora, face a aprovação, fica a candidata, apta a receber o Grau de Doutor em Odontologia desde que tenha cumprido as exigências estabelecidas de acordo com o Regimento Interno do Curso, cabendo a Universidade Federal de Pernambuco através de sua Pró-Reitoria para Assuntos de Pesquisa e Pós-Graduação, tomar as providências cabíveis. Nada mais havendo a tratar, o Presidente da Banca Examinadora encerrou a sessão e para constar foi lavrada a presente ata que vai por mim assinada , Oziclere Sena de Araújo e pelos demais componentes da Banca Examinadora e pela recém formada Doutora pela UFPE. ANDREZA BARKOKEBAS SANTOS DE FARIA .

Recife, 26 de fevereiro de 2014

Profa. Drª. ALESSANDRA DE ALBUQUERQUE TAVARES CARVALHO Doutoranda:
**Presidente**

Profa. Drª. SANDRA CONCEIÇÃO MARIA VIEIRA
**1º Examinador**

Prof. Dr. EMANUEL SÁVIO DE SOUZA ANDRADE
**2º Examinador**

Profa. Drª. LÚCIA CARNEIRO DE SOUZA BEATRICE
**3º Examinador**

Prof. Dr. LUIZ ALCINO MONTEIRO GUEIROS
**4º Examinador**

***A Deus*** *pela vida e por uma família abençoada*

***Aos meus pais Myrian e Newton (in memorian)*** *pela estrutura e amor*

***Ao meu marido Roberto*** *pelo amor, dedicação e companheirismo*

***Ao meu filho Newton,*** *grande amor da minha vida, pelo sorriso de cada dia!*

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*Especialmente aos pacientes pela disposição em participar da pesquisa, mesmo diante de uma situação difícil e de grande desafio a ser superado.*

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*Por fim, a todos que direta ou indiretamente tenham contribuído para que eu possa ter chegado até aqui.*

## RESUMO

**Introdução:** Apesar da mucosite oral ser descrita como a complicação oral mais freqüentemente associada à terapia antineoplásica pouco se sabe sobre sua etiologia e a influência na qualidade de vida dos pacientes.

**Objetivo:** O objetivo deste estudo foi avaliar a soroprevalência de herpes vírus HSV -1, EBV e CMV e a presença e severidade da mucosite oral em crianças com diagnóstico de Leucemia Linfóide Aguda (LLA) bem como avaliar o impacto da mucosite oral na qualidade de vida dos pacientes jovens diagnosticados com câncer, que desenvolveram mucosite oral quimio e/ou radio-induzida.

**Métodos:** No primeiro estudo, noventa e dois pacientes diagnosticados com LLA foram avaliados. A classificação da intensidade da mucosite foi realizada de acordo com os critérios de toxicidade estabelecidos pelo National Cancer Institute. No segundo, o grupo foi composto por uma amostra de 60 pacientes, com idade entre 14 e 20 anos, diagnosticados com câncer, que desenvolveram mucosite oral durante o tratamento. Foi utilizado o instrumento Oral Health Impact Profile (OHIP-14), composto por sete dimensões: limitação funcional, dor física, desconforto psicológico, deficiência física, deficiência psicológica, inabilidade social e incapacidade.

**Resultados:** 70,7% dos pacientes apresentaram mucosite no 7 º dia e, destes, 60% foram classificados como grau I e 40% como grau II; dos 92 indivíduos testados, 59 (64,1%) apresentaram anticorpos para HSV-1, 57 (62%) para o EBV, 75 (81,5%) para CMV_IgG e 21 (22,8%) para CMV_IgM. Utilizando o modelo de regressão logística, a presença de HSV - 1 foi 4,10 vezes maior na mucosite de Grau II do que no grau I ($p = 0,03$). No segundo estudo, a dor física atingiu a maior pontuação (pior qualidade de vida) entre as dimensões estudadas 60,8 % (292/480), seguida por limitação física 52,7% (253/480) e desconforto psicológico 50,8 % (244/480). Houve diferença estatisticamente significante em relação a sexo ($p=0,021$) para a dor física, com maior impacto entre os pacientes do sexo masculino

**Conclusão:** Com base nos resultados deste estudo, foi possível concluir que a infecção pelo vírus da herpes HSV -1, EBV e CMV é ubíquota na população estudada e que HSV-1 pode ser um fator de risco para o agravamento da gravidade da mucosite. Por outro lado,a mucosite oral é um importante efeito colateral agudo que resulta em diminuição da qualidade de vida dos pacientes com câncer.



Palavras-chave: Leucemia Linfóide Aguda. mucosite. herpesvírus. qualidade de vida. câncer.

## ABSTRACT

**Introduction:** Although oral mucositis has been described as the oral complication most frequently associated with antineoplastic therapy. Little is known about its influence on the quality of life of patients. **Objective:** The aim of this study was to evaluate the seroprevalence of herpes viruses HSV-1, EBV and CMV and presence of oral mucositis in children diagnosed with ALL and to evaluate the impact of oral mucositis on the oral health-related quality of life (OHRQoL) of patients diagnosed with cancer, who developed chemotherapy- and/or radiotherapy-induced oral mucositis..

**Methodology:** In the first study, ninety-two patients diagnosed with ALL were evaluated. Classification of mucositis intensity was performed according to toxicity criteria established by the National Cancer Institute. In the second study, the group comprised a sample of 60 patients with an age-range between 14 and 20 years, diagnosed with cancer, who developed oral mucositis during the treatment. The instrument Oral Health Impact Profile (OHIP-14) composed of seven dimensions was used: Functional limitation, physical pain, psychological discomfort, physical deficiency, psychological deficiency, social incapacity and deficiency.

**Results:**70.7% of the patients presented mucositis on the 7th day, and of these, 60% were classified as Grade I and 40% as Grade II; of the 92 individuals tested, 59 (64.1%) presented antibodies for HSV-1, 57 (62%) for EBV, 75 (81.5%) for CMV_IgG and 21 (22.8%) for CMV_IgM. Using a logistic regression model, the presence of HSV-1 was observed to be 4,10 times greater in Grade II mucositis severity than in Grade I *(p=0.03)*. In the second study, physical pain attained the highest score (worst quality of life) among the studied dimensions 60,8% (292/480), followed by physical limitation 52,7% (253/480) and psychological discomfort 50,8% (244/480). There was statistically significant difference as regards gender (*p=0.021)* for physical pain, with greater impact among patients of the male gender.

**Conclusion:** Based on the findings of this study, it was possible to conclude that infection by the herpes viruses HSV-1, EBV and CMV is ubiquitous in the studied population, and that HSV-1 may be a risk factor for aggravating the severity of mucositis. Additionally, oral mucositis is an important acute side effect that results in diminishing the OHRQoL of the patient with cancer.



Key Words: Acute Lymphoid Leukemia. mucositis. herpes vírus. quality of life. câncer.

## LISTA DE TABELAS, QUADRO E FIGURAS

***ARTIGO 1***

**TABELAS**



**QUADRO**



***ARTIGO 2***

**TABELAS**



**FIGURAS**

**LISTA DE ABREVIATURAS E SIGLAS**

| | |
|---|---|
| LLA | Leucemia Linfóide Aguda |
| HSV | Vírus Herpes simples |
| EBV | Vírus Epstein Bar |
| CMV | Citomegalovírus |
| NCI | National Cancer Institute |
| ELISA | Linked Immuno Sorbent Assay |
| LACEN | Laboratório Central do Estado |
| mL | Mililitro |
| EDTA | Ácido Etilenodiamino Tetracético |
| TNF-α | Fator-α de necrose tumoral |
| IL-1β | Interleucina 1 beta |
| IL-6 | Interleucina 6 |
| CEP | Comitê de Ética em Pesquisa |
| OHIP | Oral Heath Impact Profile |
| SPSS | Statistical Package for the Social Sciences |

## SUMARIO

## 1.APRESENTAÇÃO

Essa Tese foi estruturada sob a forma de artigos científicos para serem enviados a revistas especializadas na área de Odontologia. Os dois artigos foram formulados, segundo a proposição deste estudo, para o Journal of Oral Pathology & Medicine. O primeiro, intitulado **"Seroprevalence of herpes virus associated with the presence and severity of oral mucositis in children diagnosed with acute lymphoid leukemia"** foi aceito, encontra-se publicado no Pubmed Medline (J Oral Pathol Med. 2013 Dec 10. doi: 10.1111/jop.12138) e tratou-se de um estudo de prevalência cujo propósito foi avaliar a associação entre herpesvírus HSV-1, EBV, CMV *e* mucosite oral em crianças diagnosticadas com leucemia linfóide aguda. O segundo, intitulado "**Impact of oral mucositis on oral health-related quality of life of patients diagnosed with cancer"** foi enviado à revista supracitada e está em fase de revisão. Nesse trabalho, foi utilizado o Oral Health Impact Profile (OHIP), um importante instrumento no estabelecimento de melhores abordagens para atendimento integral ao paciente, pois permite indicar as dimensões da qualidade de vida afetadas pela condição de saúde bucal. Neste contexto, o presente trabalho apresenta sua relevância e configura um valioso conjunto de informações à comunidade científica.

## *2. ARTIGO 1*

# SEROPREVALENCE OF HERPES VIRUS ASSOCIATED WITH THE PRESENCE AND SEVERITY OF ORAL MUCOSITIS IN CHILDREN DIAGNOSED WITH ACUTE LYMPHOID LEUKEMIA

**Publicado em (J Oral Pathol Med. 2013 Dec 10. doi: 10.1111/jop.12138)**

## 2.1 RESUMO

**Introdução:** Leucemia Linfóide Aguda (LLA) é a neoplasia hematológica mais comumente diagnosticada em crianças. Entre os efeitos colaterais secundários da quimioterapia a mucosite é a complicação mais frequente . O objetivo deste estudo foi avaliar a soroprevalência de herpes vírus HSV -1, EBV e CMV e a presença e severidade da mucosite oral em crianças com diagnóstico de LLA.

**Metodologia:** Noventa e dois pacientes diagnosticados com LLA foram avaliados. As amostras de soro foram testadas pelo método ELISA. A presença de mucosite foi observada no primeiro dia antes da terapia antineoplásica (D0) e no sétimo dia (D7) pós-terapia. A classificação da intensidade da mucosite foi realizada de acordo com os critérios de toxicidade estabelecidos pelo National Cancer Institute.

**Resultados:** 70,7% dos pacientes apresentaram mucosite no 7 º dia e, destes, 60% foram classificados como grau I e 40% como grau II; dos 92 indivíduos testados, 59 (64,1%) apresentaram anticorpos para HSV-1, 57 (62%) para o EBV, 75 (81,5%) para CMV_IgG e 21 (22,8%) para CMV_IgM. Utilizando o modelo de regressão logística, a presença de HSV - 1 foi 4,10 vezes maior na mucosite de Grau II do que no grau I (*p = 0,03)*.

**Conclusão:** Com base nos resultados deste estudo, foi possível concluir que a infecção pelo vírus da herpes HSV -1, EBV e CMV é ubíquota na população estudada e que HSV- 1 pode ser um fator de risco para o agravamento da gravidade da mucosite .

Palavras-chave: Leucemia Linfóide Aguda; mucosite; herpesvírus.

## 2.1 ABSTRACT

**Introduction:** Acute Lymphoid Leukemia (ALL) is the hematologic neoplasia most commonly diagnosed in children. Among the secondary side effects of chemotherapy, mucositis is the most frequent complication. The aim of this study was to evaluate the seroprevalence of herpes viruses HSV-1, EBV and CMV and presence of oral mucositis in children and adolescents diagnosed with ALL**.**

**Methodology:** Ninety-two patients diagnosed with ALL were evaluated. Serum samples were tested by ELISA method. Presence of mucositis was observed on the first day before antineoplastic therapy (D0) and on 7th day post-therapy. Classification of mucositis intensity was performed according to toxicity criteria established by the National Cancer Institute.

**Results:**70.7% of the patients presented mucositis on the 7th day, and of these, 60% were classified as Grade I and 40% as Grade II; of the 92 individuals tested, 59 (64.1%) presented antibodies for HSV-1, 57 (62%) for EBV, 75 (81.5%) for CMV_IgG and 21 (22.8%) for CMV_IgM.Using a logistic regression model, the presence of HSV-1 was observed to be 4,10 times greater in Grade II mucositis severity than in Grade I *(p=0.03)*.

**Conclusion:**Based on the findings of this study, it was possible to conclude that infection by the herpes viruses HSV-1, EBV and CMV is ubiquitous in the studied population, and that HSV-1 may be a risk factor for aggravating the severity of mucositis.

Key Words: Acute Lymphoid Leukemia; mucositis; herpes virus.

## 2.2 INTRODUCTION

It is estimated that the incidence of pediatric tumors in the world ranges from 1% to 3% of the total number of cases of cancer. In Brazil in 2012, with the exception of non melanoma skin tumors, the estimated number of new cases of cancer was 384,340, it follows therefore, that there will be around 11,530 new cases of cancer in children and adolescents up to the age of 19 years (1).

Acute Lymphoid Leukemia (ALL) is the most common hematologic neoplasia in children (2-5) it represents 75% of all the childhood acute leukemias and its peak prevalence is in children between 2 and 5 years of age (6). They are primary neoplasias of the bone marrow, characterized by an accumulation of lymphoblasts (undifferentiated cells) to the detriment of mature lymphocytes in the peripheral blood, bone marrow, thymus and lymph nodes (7).

They are classified according to their histogenesis, primary hematopoietic cell affected (myeloid or lymphoid) and their clinical behavior (acute or chronic) (8-10). The frequency of incidence in the population from 0 to 14 years, is 1/25,000 individuals/year and the risk for developing the disease in the first 10 years is 1/2,880. ALL is more common in white children than in Afro-descendant/black children (1,8:1), and in boys than in girls (1,2:1) (8,11).

The etiology has not yet been determined, although the following have been emphasized as possible causes: effects of irradiation, exposure to antineoplastic drugs, associated genetic and immunologic factors, and exposure to some viruses (12-15). Due to the immunosuppression caused by antineoplastic therapy some

clinical complications are expected in children submitted to chemotherapy or radiotherapy during treatment (16).

Among the secondary side effects of chemotherapy, mucositis is the most common complication of the cytotoxicity caused by chemotherapy and radiotherapy (17-30)and its estimated prevalence is between 30% and 75%(31).

Oral mucositis results from the direct inhibitory effect of the chemotherapy drugs on mucosal cell replication and proliferation, which promotes a reduction in the capacity of renovation of the basal layer of the epithelium. These events favor atrophy of the mucosa, accentuated reduction in collagen production and eventual ulceration (32). The release of substances in the conjunctive tissue, which exacerbate the inflammatory response, added to the epithelial alterations, complete the pathogenesis of mucositis,which is characterized by five stages: onset, regulation, amplification, ulceration and healing (33).

The toxic effects of chemotherapy on the oral mucosa being soon after its administration, attaining peak intensity between the 7th and 10th day after beginning with the chemotherapy cycle, with resolution occurring in less than two weeks (34).

In patients with Acute Lymphoid Leukemia (ALL) this secondary effect is related with a frequency ranging from 18 to 33% (35-37). The immunosuppression secondary to chemotherapy treatment favors the occurrence of infections by opportunist agents, such as for example, fungi and high seroprevalence of herpes viruses (17,21,38-40) resulting in diminished quality of life of the irradiated patient (41,42)**.**

Oral infections by herpes viruses are very common, with emphasis on HSV-1, which is manifested as a necrotizing ulcerative lesion in approximately 40 to 70% of the patients (43). Its occurrence represents a significant risk factor for systemic infections, particularly in neutropenic patients (44,45).

The purpose of this study was to evaluate the seroprevalence of herpes viruses HSV-1, EBV and CMV and presence of oral mucositis in children and adolescents diagnosed with ALL**.**

## 2.3 METHODOLOGY

A cross-sectional study was conducted, and was approved by the Research Ethics Committee CEP/CCS/UFPE N.148/2011 with SISNEP FR – 408010 registration. The participants in the research signed a Term of Free and Informed Consent; they were examined and their data were filled out on a Clinical Record Chart. A total of 92 patients diagnosed with Acute Lymphoid Leukemia were evaluated; they had not undergone previous treatment, and were consecutively admitted to the Pediatric Oncology Service of the "Instituto de Medicinal Integral Prof. Fernando Figueira (IMIP)", in the period from August 2011 to September 2012. For sample calculation, the EpiInfo program was used, and an error of 6% was adopted.

All the patients with the diagnosis of ALL were followed up by the oncologist doctors and by the researcher responsible for the study. During the period of hospitalization, the patients included in the study were evaluated with the aim of identifying and classifying the episodes of oral mucositis.

The Kappa test of agreement and the intra- and inter-observer integrity were performed for two dental residents, who were being monitored by an experienced dentist belonging to the service. This process took place during sessions of discussion lasting 2h and training for 3 days ($k$=0.79). Evaluations with regard to the presence of mucositis were performed on the first day before antineoplastic therapy (D0) and on 7th day post-therapy.

Classification of the intensity of mucositis was performed in accordance with the toxicity criteria established by the National Cancer Institute (NCI), version 3.0 (46), in which five grades are defined, and briefly summarized in Chart 1.

***Collection of Material for Identification of Herpes Viruses***

Approximately 10ml of total blood were collected from the participants, in tubes containing EDTA. The blood samples collected were stored at a temperature of approximately 5 degrees Celsius, for a maximum of 48 hours. Afterwards, these were centrifuged, the serum was separated and analyzed for the presence of antibodies. The serum samples were evaluated by means of the *Enzyme Linked Immuno Sorbent Assay* (ELISA) method, using commercial kits of the *Human GmbH* brand, for processing the samples.

The clinical-laboratory information collected was stored on the research form, specifically developed for this study, and the samples were processed in the Central Laboratoryof Pernambuco (“Laboratório Central de Pernambuco – LACEN”).

***Data Analysis***

For inferential statistical analysis of the variables *herpes viruses* and *presence of mucositis* the Pearson Chi-square test was used, and the level of significance of 5% was adopted. A multivariate analysis was performed, using the binary logistic regression model to evaluate the association between the degrees of severity of mucositis and herpes viruses. Hosmer-Lemeshow statistics were used to verify the quality of adjustment of the model. The data were typed into an Excel spreadsheet and the software program used to obtain the statistical calculation was SPSS (Statistical Package for Social Sciences) version 17.0.

**2.4 RESULTS**

Ninety-two patients were followed-up during the research, with 53.3% being of the male sex and 46.7% of the female sex, with the median age of 6 years, ranging between 2 and 10 years.

Around 65 (70.7%) of the patients presented mucositis on the 7th day, and of these, 39 (60%) were classified as Grade I and 26 (40%) as Grade II; of the 92 individuals tested, 59 (64.1%) presented antibodies for HSV-1, 57 (62%) for EBV, 75 (81.5%) for CMV_IgG and 21 (22.8%) for CMV_IgM; around 9.8% presented concomitant seroprevalence positive for three types of viruses; 56.5% presented HSV-1 and CMV_IgG together, as shown in Table 01.

As regards the prevalence of herpes viruses due to the presence of mucositis, it may be emphasized that there was a higher percentage, 85.7%, of CMV_IgM and HSV-1+CMV_IgM viruses which, together presented mucositis, however, in no combination of viruses was there statistically significant difference, as shown in Table 02.

Of the 92 patients in the sample, 89 (96.7%) presented at least one type of virus, as may be observed in Table 03, which correlates the quantity of viruses per patient in relation to the presence of mucositis. The 3 (3.3%) patients who did not present any type of virus, presented Grade I mucositis on the 7th day. However, there was no statistically significant difference between the presence of mucositis in comparison with the quantity of viruses present in the studied population.

A multivariate analysis was performed using a binary logistic regression model. Hosmer-Lemeshow statistics were used to verify the quality of adjustment of the model. The Wald test verified the significance if each variable individually, and in the model in the present research, two variables were significant, as shown in Table 4.

The variable considered a risk factor for the severity of mucositis, in the multivariate logistic regression analysis, was the virus HSV-1 (OR=4.102; IC:1.149-14.651; *p=0.03*), and as a protective variable the virus CMV (OR=0.248; IC:0.062-0.9991; p=0.049), that is to say: in the logistic model the presence of HSV-1 was 4.10 times greater in Grade II severity of mucositis than in Grade I *(p=0.03)* and there were 75.2% chances of the presence of CMV not occurring in the group with Grade II type of severity (*p=0.049)*.

## 2.5 DISCUSSION

Although seroepidemiological studies have pointed out that over 90% of the world population have serum antibodies against at least one of the strains of HSV (47) only 40% of these individuals have sensitivity for the development of secondary herpetic manifestations (48). For Wade et al. (1989) up to 60% of the

individuals with serology positive for HSV present asymptomatic or oligosymptomatic conditions not recognized by the patients themselves (49).

Previous studies by Elad et al. (2010) have proposed recommendations based on evidences for the prevention and treatment of oral viral infections in patients with cancer. The available studies mainly refer to the infections by HSV-1, and to a lesser extent, to other members of the Herpesviridae family.

The relations between viral infectious diseases and ALL continue to be a question of interest and speculation. The results of serological tests in the studies of Djuric et al.(2009) have shown that 91.7% of the individuals were seropositive for HSV-1. In addition, the studies of Tesse et al.(2009) have affirmed that the seroprevalence of IgG antibodies for HSV and CMV in Leukemic children was significantly higher than it was in the controls. A similar observation was made by Loutfy et al.(2006)in Egyptian children, although their results were not statistically significant. These findings corroborate the results of the present research with regard to the high seroprevalence of HSV, and particularly of CMV in the studied population.

Shlehofer et al. (1996) also added that the seroprevalence of IgG EBV antibodies tends to be greater in children with ALL than in healthy individuals, and in our findings the prevalence of EBV was considered high and practically the same as that of HSV. There is strong correlation between latent infection by EBV - responsible for infectious mononucleosis in humans - and the development of different malignant tumors, such as Burkitt's lymphoma, Hodgkin’s disease, Lymphoma B and nasopharyngeal carcinoma. Proteins expressed by EBV act directly as oncogenes, stimulating proliferation of the infected cells. In spite of no

description in the literature correlating the presence of this virus with the aggravation of chemotherapy-induced oral mucositis, its participation as co-factor in immunosuppressed patients has not been discarded (52).

Whereas, the studies of Lalla et al. (2008) and Nicolatou-Galitis et al. (2006) have related a positive correlation between the occurrence of severe oral mucositis and the presence of HSV 1. These findings are in alignment with the results of the present research, which demonstrated that infection by HSV was a risk factor for aggravation of the severity of mucositis, as the presence of HSV-1 was 4.10 times greater in Grade II than in Grade I mucositis, and was shown to be statistically significant by means of a logistic regression model.

However, Redding et al. (1998) obtained no correspondence between the presence of the HSV 1 virus and the degrees of severity of oral mucositis, in addition to not obtaining a satisfactory response to the use of antiviral agents in the studied populations.

An explanation for the discrepancy of these findings may be found in the population of patients involved. The majority of studies that refer to HSV 1 as a co-factor in the aggravation of mucositis lesions, involve patients submitted to schemes of chemotherapy that include immunosuppressive drugs, with the possible appearance of neutropenia.

Moreover, it has been suggested that it is possible that HSV might have behaved as a risk factor due to the fact that its latency occurs in the sacral and trigeminal ganglia, which may serve as epicenter in the clinical recurrences, thus aggravating the degree of mucositis. Therefore, HSV-1 could modulate the immune

response and collaborate in triggering more complicated clinical problems than those observed in immunocompetent individuals (56). Whereas, the latency of CMV occurs in the cells of salivary glands, endothelium and in macrophages, and in spite of having presented a higher prevalence, it did not contribute to the aggravation of mucositis, however, its participation as a possible co-factor responsible for this, has not been discarded.

With regard to the toxic effects of chemotherapy on the oral mucosa, studies have related that they begin soon after administration of this therapy, attaining a peak intensity between the 7th and 10th day after beginning the chemotherapy cycle, with resolution occurring in less than two weeks (34,43) this finding confirms the present study, in which 70,7% of the studied population presented mucositis on the 7$^{th}$ day post-antineoplastic therapy, and reiterated by the studies of Djuric et al. (2009) who demonstrated that 60% of the patients with ALL developed mucositis. These results are in agreement with the previous studies of Djuric et al. (2006) who reported the presence of mucositis in around 58-64% of the studied patients, and are aligned with the findings of CHAN et al.(2003) who related that 12.8% of the patients presented mucositis on day 1; 58.5% on day 8, and 42.5% in 16 days of chemotherapy. Furthermore, Bonan et al. (2005)and Trotti et al (2003) added that for the majority of patients, 10 to 14 days are sufficient for repairing the lesioned tissue.

Based on the findings of this study, it was possible to conclude that infection by the herpes viruses HSV-1, EBV and CMV is ubiquitous in the studied population, and that HSV-1 may be a riskfactor for aggravating the severity of mucositis.

## CONFLICT OF INTEREST:

The  authors declare that there was no conflict of interests.

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TABLES

**Table 01 – Description of gender, presence of mucositis, mucositis grading and presence of herpesvirus**

| Variables | n | % |
|---|---|---|
| SEXO | | |
| Male | 49 | 53,3 |
| Female | 43 | 46,7 |
| PRESENCE OF MUCOSITIS ON 7TH DAY(n=92) | 65 | 70,7 |
| CLASSIFICATION OF MUCOSITIS ON 7TH DAY (n=65) | | |
| I | 39 | 60,0 |
| II | 26 | 40,0 |
| **TYPES OF HERPESVÍRUS (N=92)** | | |
| HSV-1 | 59 | 64,1 |
| EBV | 57 | 62,0 |
| CMV_IgG | 75 | 81,5 |
| CMV _IgM | 21 | 22,8 |
| HSV1+EBV | 41 | 44,6 |
| HSV1+CMV_IgG | 52 | 56,5 |
| HSV1+CMV_IgM | 14 | 15,2 |
| EBV+CMV_IgG | 47 | 51,1 |
| EBV+CMV_IgM | 14 | 15,2 |
| HSV1+EBV+CMV_IgG | 37 | 40,2 |
| HSV1+EBV+CMV_IgM | 10 | 10,9 |
| EBV+CMV_IgG+CMV_IgM | 12 | 13,0 |
| HSV1+CVM_IgG+CVM_IgM | 13 | 14,1 |
| HSV1+EBV+CMV_IgG+CMV_IgM | 9 | 9,8 |

**Table02-Correlation between the occurrence of oral mucositis and the presence of herpes virus in pediatric patients with leukemia.**

| Herpesvírus | Presence of mucositis on 7th day | | | | Full | | p-value* |
|---|---|---|---|---|---|---|---|
| | No | | Yes | | | | |
| | n | % | n | % | n | % | |
| HSV-1 | 18 | 30,5 | 41 | 69,5 | 59 | 100 | 0,469 |
| EBV | 16 | 28,1 | 41 | 71,9 | 57 | 100 | 0,454 |
| CMV_IgG | 24 | 32,0 | 51 | 68,0 | 75 | 100 | 0,192 |
| CMV _IgM | 3 | 14,3 | 18 | **85,7** | 21 | 100 | 0,069 |
| HSV1+EBV | 12 | 29,3 | 29 | 70,7 | 41 | 100 | 0,586 |
| HSV1+CMV_IgG | 17 | 32,7 | 35 | 67,3 | 52 | 100 | 0,285 |
| HSV1+CMV_IgM | 2 | 14,3 | 12 | **85,7** | 14 | 100 | 0,152 |
| EBV+CMV_IgG | 13 | 27,7 | 34 | 72,3 | 47 | 100 | 0,446 |
| EBV+CMV_IgM | 3 | 21,4 | 11 | 78,6 | 14 | 100 | 0,360 |
| HSV1+EBV+CMV_IgG | 11 | 29,7 | 26 | 70,3 | 37 | 100 | 0,564 |
| HSV1+EBV+CMV_IgM | 2 | 20,0 | 8 | 80,0 | 10 | 100 | 0,390 |
| EBV+CMV_IgG+CMV_IgM | 3 | 25,0 | 9 | 75,0 | 12 | 100 | 0,509 |
| HSV1+CVM_IgG+CVM_IgM | 2 | 15,4 | 11 | 84,6 | 13 | 100 | 0,197 |
| HSV1+EBV+CMV_IgG+CMV_IgM | 2 | 22,2 | 7 | 77,8 | 9 | 100 | 0,475 |

p-value=value obtainedby chi-square test with 5% significance

**Table 03 - Correlation between the presence of oral mucositis and the number detected by herpesvirus patients with childhood leukemia.**

| Number ofvirus presentper patient | Presence of mucositis on 7th day | | | | **TOTAL** | | **p-value*** |
|---|---|---|---|---|---|---|---|
| | **No** | | **Yes** | | | | |
| | **n** | **%** | **n** | **%** | **n** | **%** | |
| 1 | 7 | 25,9 | 13 | 21,0 | 20 | 22,5 | |
| 2 | 8 | 29,6 | 16 | 25,8 | 24 | 27,0 | |
| 3 | 10 | 37,0 | 26 | 41,9 | 36 | 40,4 | 0,873 |
| 4 | 2 | 7,4 | 7 | 11,3 | 9 | 10,1 | |
| **Full** | **27** | **100,0** | **62** | **100,0** | **89** | **100,0** | |

p-value=value obtainedby chi-square test with 5% significance

**Table 04 - Final model of logistic regression on the severity II in severity I considering herpesviruses HSV-1 and EBV, CMV_IgG as explanatory variables**

| | B | S.E. | Wald | df | p-valor | OR (Razão de Chances) | IC 95% para OR | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower Limit | Upper Limit |
| HSV1 | 1,41 | 0,65 | 4,72 | 1 | 0,030 | 4,102 | 1,149 | 14,651 |
| CMV_IgG | -1,39 | 0,71 | 3,84 | 1 | 0,049 | 0,248 | 0,062 | 0,999 |
| EBV | 0,08 | 0,58 | 0,02 | 1 | 0,885 | 1,087 | 0,349 | 3,390 |
| Constant | -0,32 | 0,67 | 0,22 | 1 | 0,636 | 0,730 | | |
| Ajuste do modelo* | 0,495 | | | | | | | |

* adjustmentmodel by Hosmer-Lemeshow

**Chart 1.Classification of Mucositis, in accordance with the NCI, 2006.**

| Grading | Symptoms |
|---|---|
| **Grade 0 (Without mucositis)** | **Without symptoms** |
| **Grade 1** | **Erythema of the mucosa, or slight pain. Minimal respiratory symptoms, but they do not interfere functionally.** |
| **Grade 2** | **Painful erythema, edema, ulcers or pseudomembranes, but the patient is able to eat. Need for modified diet. Respiratory symptoms interfering functionally.** |
| **Grade 3** | **Painful Erythema, edema, ulcers or confluent pseudomembranes. Bleeding with the slightest trauma. The patient is unable to eat or swallow liquids adequately.** |
| **Grade 4** | **Extensive ulcers. Tissue necrosis. Significant spontaneous bleeding. Needs enteral or parenteral support. Life-threatening Risk.** |
| **Grade 5** | **Death** |

Common Terminology Criteria for Adverse Events v3.0. Disponível em: http://ctep.cancer.gov. NCI. Publish Date: August 9, 2006.

## *3. ARTIGO 2*

# IMPACT OF ORAL MUCOSITIS ON ORAL HEALTH-RELATED QUALITY OF LIFE OF YOUNG PATIENTS DIAGNOSED WITH CANCER

## 3.1 RESUMO

**Introdução:** Apesar de mucosite oral tem sido descrita como a complicação oral mais freqüentemente associada à terapia antineoplásica pouco se sabe sobre sua influência na qualidade de vida dos pacientes.

**Objetivo:** Avaliar o impacto da mucosite oral na qualidade de vida (OHRQoL) dos pacientes diagnosticados com câncer, que desenvolveram mucosite oral quimio e/ou radio-induzida.

**Métodos:** O grupo de estudo foi composto por uma amostra de 60 pacientes, com idade entre 14 e 20 anos, diagnosticados com câncer, que desenvolveram mucosite oral durante o tratamento. Foi utilizado o instrumento Oral Health Impact Profile (OHIP-14), composto por sete dimensões: limitação funcional, dor física, desconforto psicológico, deficiência física, deficiência psicológica, inabilidade social e incapacidade. **Resultados:** A consistência interna do OHIP-14 foi mensurada pelo coeficiente alfa de Cronbach (*alfa=0,76*). A dor física atingiu a maior pontuação (pior qualidade de vida) entre as dimensões estudadas 60,8 % (292/480 ), seguida por limitação física 52,7% (253/480) e desconforto psicológico 50,8 % (244/480). A dimensão 'Limitação social " obteve a menor pontuação 27,2 % (131/480). Houve diferença estatisticamente significante em relação a sexo (*p=0,021*) para a dor física, com maior impacto entre os pacientes do sexo masculino **Conclusão:** A mucosite oral é um importante efeito colateral agudo que resulta em diminuição da OHRQoL dos pacientes com câncer.

Palavras -chave: Qualidade de vida; mucosite; câncer

## 3.1 ABSTRACT

**Introduction:** Although oral mucositis has been described as the oral complication most frequently associated with antineoplastic therapy. Little is known about its influence on the quality of life of patients. **Objective:** To evaluate the impact of oral mucositis on the oral health-related quality of life (OHRQoL) of patients diagnosed with cancer, who developed chemotherapy- and/or radiotherapy-induced oral mucositis. **Methods:** The study group comprised a sample of 60 patients with an age-range between 14 and 20 years, diagnosed with cancer, who developed oral mucositis during the treatment. The instrument Oral Health Impact Profile (OHIP-14) composed of seven dimensions was used: Functional limitation, physical pain, psychological discomfort, physical deficiency, psychological deficiency, social incapacity and deficiency. **Results:** The internal consistency of OHIP-14 mesuared by the Chronbach's alpha coefficient was of 0.76. Physical pain attained the highest score (worst quality of life) among the studied dimensions 60,8% (292/480), followed by physical limitation 52,7% (253/480) and psychological discomfort 50,8% (244/480). The dimension 'social limitation' obtained the lowest score 27,2% (131/480). There was statistically significant difference as regards gender (*p=0.021)* for physical pain, with greater impact among patients of the male gender. **Conclusion:** Oral mucositis is an important acute side effect that results in diminishing the OHRQoL of the patient with cancer.

**Key Words: Quality of life, mucositis, cancer**

## 3.2 INTRODUCTION

The assessment of oral health-reported quality of life (OHRQoL) has become an integral part of evaluating oral health programs. Traditional dental indicators alone (with no information on oral wellbeing) are insufficient. It is therefore important to measure the physical and psychosocial impact of oral health. However, relationships between biological or clinical variables and health-related quality of life are mediated by a variety of personal, social, environmental and cultural circumstances.

Comorbidities associated with various cancer therapies are longer in list which adversely affect patients' QoL(1). Oral mucositis (OM) is considered one of the most stressful acute reaction during CRT (2-15). OM-associated pain significantly impairs oral functions including phonation, deglutition, dysgeusia among other. The continuous thick viscid secretions caused by severe OM add additional burden to the patient in terms of coughing, aspiration, and disturbed sleep. OM also increases the risk of infections and septicemia. Severe OM can cause increased narcotic analgesics use, increased hospitalization/ prolonged hospital stay, and invasive form of nutritional support. Sometimes severe OM can also cause unplanned treatment interruptions (16)

Additionaly, the prevalence of chemotherapy-induced mucositis has been shown to vary between 30% and 75% of patients, depending on the type of treatment (17)**,** and the risk of developing lesions of the mucosa increases with the number of chemotherapy cycles and previous episodes of mucositis (6,12,18). In around 50% of patients with mucositis, the lesions may be serious, causing significant pain, interfering in nutrition, and frequently demanding a change in the

chemotherapy regime (16). In addition, mucositis may predispose the patient to fungal, viral and bacterial infections, and may result in risks for systemic infection (4-6,12).

Chemotherapy-induced mucositis is more common in hematological cancer, in which there is myelosuppression, and a more prolonged scheme of therapy, since mucositis induced by radiation is more common in cancer of the head and neck, because of the direct irradiation in the oral cavity, depending on the dose and type of radiation (12,19)**.** Over the course of the last decade, there was a dramatic increase in the use of quality of life measurements in clinical trials (20-23). The oral health impact profile (OHIP) is an instrument designed to measure oral-health-related QoL. The shortform of OHIP (OHIP-14) is reported to be a useful instrument for use in a clinical setting with good reliability, validity and precision (24).

The questionnaire is designed to measure self-reported dysfunction, discomfort and disability attributed to oral conditions, and is based on a conceptual oral health model (25). Additionally, this instrument was used to measure the oral health related QoL in the patients with Behçet's disease, RAS (26) and keratosis, ulcers, lichen planus, candidiasis, dry mouth, burning mouth, temporomandibular disorders and pain finding that diseases of the oral mucosa can have a serious impact on the patients' oral quality of life (27).

It has been demonstrated that evaluation of the quality of life in patients diagnosed with cancer could contribute to an improvement in the treatment and even in the prognosis (28-34). Evaluation of the effect of oral diseases and social conditions may be of great value to researchers, health care planners and care

providers (35-37). Above all, studies about the quality of life may guide professionals in more effective treatment of patients with cancer.

In view of the foregoing, the aim of this study was to evaluate the impact of oral health on the OHRQoL of patients diagnosed with cancer, who developed chemotherapy- and/or radiotherapy-induced oral mucositis.

**3.3 METHODS**

This is a cross-sectional study, in which a convenience sample of 60 patients, between 14 and 20 years, who developed oral mucositis during cancer treatment were invited to participate, in the period from August to December 2011. The study was conducted at the Institute of Integral Medicine "Professor Fernando Figueira" (IMIP), Recife, Brazil and obtained approval from the Human Research Ethics Committee protocol CEP/CCS/UFPE N.148/2011 registered with SISNEP FR – 408010. The participants signed an Informed Consent Form before data collection.

Electronic record charts of patients diagnosed with oral mucositis were selected, and the patients were interviewed during the treatment period or at the consulting rooms during return visits. The Kappa test of agreement and the intra- and inter-observer integrity were performed for two dental residents, who were being monitored by an experienced dentist belonging to the service. This process took place during sessions of discussion lasting 2h and training for 3 days ($k$=0.79).

The instrument OHIP-14 comprised seven dimensions was used. These dimensions are: functional limitation, physical pain, psychological discomfort, physical deficiency, psychological deficiency, social incapacity and deficiency. The

dimension *functional limitation* included questions about the difficulty with speaking, and worsening in the taste of foods; in the pain dimension, they were asked about the sensation of pain and discomfort when eating; in the dimension *psychological discomfort*, the questions were with reference to concern and stress about the oral condition. The harm caused to eating and the need to have to stop eating were the requisites in the dimension *physical inability*, while in *psychological inability* the questions referred to the difficulty with relaxing and the feeling of shame because of the oral condition. The dimension *social inability* included questions about irritation with other persons and difficulty with performing daily routine activities because of the oral condition; and the questions comprised by the dimension *incapacity* sought to find out whether the perception of the quality of life had worsened, and whether the person felt completely incapable of developing his/her routine activities (36).

There were five options of responses with a code for each of the fourteen questions: Never (0), Rarely (1), Sometimes (2), Repeatedly (3) and Always (4). All of the problems were evaluated based on the last six months. The OHIP-14 scale ranged from 0 to 56 points and the higher the score, the worse was the quality of life (36,37).

**Statistical Analysis**

The data were typed into an Excel spreadsheet and the software program used to obtain the statistical calculation was SPSS (Statistical Package for Social Sciences) version 17.0. As a result of the asymmetrical distribution of the OHIP scores, the Exact Fisher test was used, and values lower than 0.05 were accepted as being significant.

**Reliability**

The reliability was evaluated by internal consistency and stability tests. The degree of homogeneity of the scale was evaluated by Chronbach's alpha, which is a summary statistic that captures de degree of agreement between the possible subsets of questions (38). The coefficient has the following scales: a≤0.30 very low; 0.30<to≤0.60 low; 0.60<to≤0.75 moderate; 0.75<to≤0.90 high and a>0.90 very high (38)**.**

**3.4 RESULTS**

A sample of 60 patients, with an age-range between 14 and 20 years, mean age 15.8, of whom 45% were of the female gender. The instrument OHIP-14 used to measure the impact of oral health on the quality of life, may attain a score between 0 and 56 points, and the lower the total score obtained, the less the impact on quality of life, therefore, the greater the patient's satisfaction and wellbeing.

In this study, the majority of patients, 35%, obtained between 20 and 30 points; 25% between 30 and 40, and only 3.3% between 41 and 56 points, as may be seen in Figure 1. The distribution of patients according to diagnosis may be observed in Table 1.

In the OHIP-14 questionnaire, every two questions correspond to a dimension, and the score of each dimension is given by the sum of the values of the two corresponding questions. Considering that each question may attain the maximum weight of 4 (with reference to the response "always") and considering the studied sample of 60 patients, the maximum possible sum of the score of a dimension would attain 480 points. Physical pain attained the highest score (worst quality of life) among the studied dimensions (292/480), followed by physical limitation

(253/480) and psychological discomfort (244/480), psychological limitation (195/480), incapacity (180/480) and functional limitation (154/480). The dimension social limitation obtained the lowest score (131/480), as may be observed in Figure 2.

The frequency of the responses related to the studied dimensions may be observed in Table 02: Functional limitation, psychological inability, social inability and incapacity obtained over 40% of responses in Code 0 (never). Only the dimension *physical pain*, 37,5%, had the highest percentage of "always" responses.

Figure 3 demonstrates the percentage distribution of patients according to the number of OHIP dimensions. None of the patients had impact on all seven dimensions simultaneously; however, 48.4% presented more than two dimensions that affected the quality of life.

Table 3 shows the distribution of patients by sex, according to the responses in the seven dimensions. There was statistically significant difference as regards gender (*p=0.021)* for physical pain, with greater impact among patients of the male gender. The internal consistency of OHIP-14 and its sub-scales were measured by Chronbach's alpha coefficient. The value of the general coefficient, considering the 14 items, presented high correlation (alpha=0.761), Table 4.

## 3.5 DISCUSSION

Chemotherapy- and Radiotherapy-induced oral mucositis, in addition to affecting the patient's quality of life, may lead to demanding partial or complete interruption of the therapy before the planned regime has been completed, thereby increasing the risk of tumor cell proliferation and making it difficult to control the cancer (39). Oral mucositis is one of the most important side effects of chemotherapy and radiotherapy, because it makes it difficult for patients to swallow food, causes alterations in taste in addition to limiting speech, chewing, and causing pain, thereby diminishing the quality of life of patients (40).

A recent report in which mouth and throat soreness data were collected in head and neck cancer (HNC) patients revealed 80% incidence of severe OM (41). In addition, a retrospective study found a 70% incidence of severe OM for HNC patients receiving radiochemotherapy (42). One probable explanation of the high incidence is the effect of direct oral mucosal injury from irradiation per se (43). These results are similar to those of Epstein et al.(1999) (1)**,** in which patients irradiated in the head and neck region related that the pain interfered directly in their daily activities and affected their quality of life. In fact, the results of the present study showed that one of the dimensions of OHIP-14 "physical pain", which corresponds to the feeling of pain and discomfort when eating, followed by the dimension "physical inability", which corresponds to harming the ability to eat and need to have to stop eating were more commonly associated with the severity of OM.

Furthermore, Kim et al (44) evaluated OM-related symptoms, including oral pain, dysphagia, oral bleeding, oral dryness, scalloping of the tongue, and

ulcerations. The subjective symptoms,including oral pain and oral dryness, were more common than objective signs, such as bleeding, scalloping of the tongue, and ulcerations. Thus, patients suffering from adverse effects involving the oral cavity more frequently than the incidence of objective oral mucosal lesions as observed by the physician (43).

According to the International Association for the study of Pain, pain is an unpleasant sensory and emotional experience secondary to tissue damage, and this definition does not differentiate the pain felt by the female sex from that felt by the male sex.

In the present study, there was statistically significant difference with regard to gender (*p=0.021)* for the dimension "physical pain" with greater impact among patient of the male gender, in which there was a higher number of "repeatedly" and "always" responses. It is possible that this occurs due to the lower pain threshold of the male sex in comparison with the female sex. However, reports in the literature have demonstrated the contrary, because diverse factors are considered responsible for the differences in perception between the sexes, with emphasis on the great prevalence of pain in the female sex, among these the biological factors, such as the sex hormones, which represent one of the main mechanisms that explain these differences in pain perception between the sexes (45).

An acceptable possibility is the heterogeneity in the diagnosis of the patients in the present study, which may have had an influence on different responses related to pain caused by mucositis. This study included bone cancer, cancer of

the head and neck, and hematological cancer, which may have produced different results.

Furthermore, greater prevalence of the female sex was observed, with regard to the dimension "social inability", which includes questions about irritation with others and difficulty with performing routine daily activities because of the oral condition, however, no statistically significant difference was observed.

In the present study, none of the patients had impact on the seven dimensions simultaneously, but in the majority of the interviewees, there was impact on more than two dimensions of the instrument OHIP-14. Mumcu et al. (26) used OHIP-14 and SF-36 to measure the oral and general health related QoL in the patients with Behçet's disease, RAS and healthy controls, and observed worse oral QoL in these patients. Additionally López-Jornet et al (27) evaluated stomatological diseases (keratosis, ulcers, lichen planus, candidiasis, dry mouth, burning mouth, temporomandibular disorders and pain) using the OHIP-14, finding that diseases of the oral mucosa can have a serious impact on the patients' oral quality of life. These findings demonstrated that the repercussions are relevant, and cannot be ignored.

Based upon the findings of the present study, it was possible to conclude that oral mucositis is an important acute side effect that results in diminishing the OHRQoL of the patient with cancer.

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Figure 1 - Percentage distribution of the result value by OHIP score range

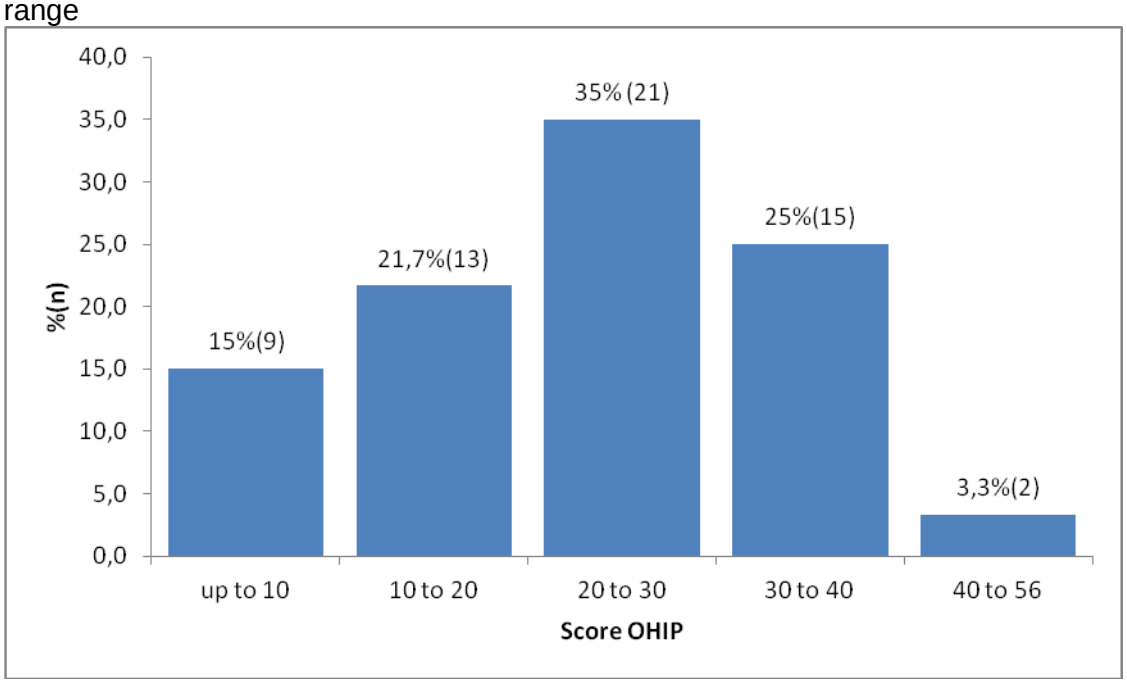

Table 1 - Distribution of patients by gender, diagnosis and treatment.

| Diagnosis | Gender | | | Treatment |
|---|---|---|---|---|
| | M | F | % | |
| Nasopharyngeal Carcinoma | 02 | | 3,3 | C + R |
| Langerhans Cell Histiocytosis | 01 | | 1,7 | C |
| Hodgkin's Lymphoma | 01 | | 1,7 | C + R |
| Non Hodgkin Lymphoma | 05 | 03 | 13,3 | C + R |
| ALL | 14 | 18 | 53,4 | C + R |
| AML | 03 | 03 | 10,0 | C |
| Neuroblastoma | 01 | | 1,7 | C + R |
| Rhabdomyosarcoma | 02 | 01 | 5,0 | C + R |
| Ewing Sarcoma | 04 | 02 | 10,0 | C + R |
| **Total** | **33** | **27** | **100** | |

C-Chemotherapy;R-radiotherapy

Figure 2 - Distribution of scores achieved by size

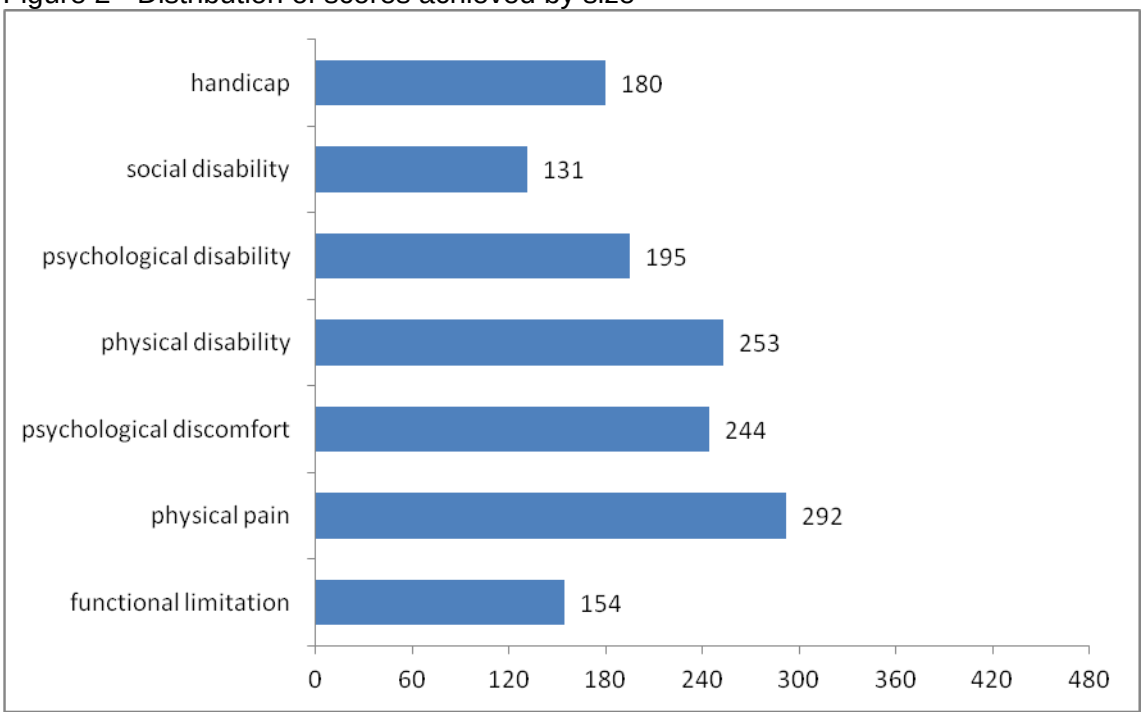

Table 2 - Percentage distribution of OHIP responses according to their size

| Dimensão OHIP | % replies | | | | | Total |
|---|---|---|---|---|---|---|
| | Never (coded 0) | Hardly ever (coded 1) | Occasionally (coded 2) | Fairly often (coded 3) | Very often (coded 4) | |
| Functional Limitation | **41,7** | 13,3 | 29,2 | 6,7 | 9,2 | 100,0 |
| Physical Pain | 15,0 | 11,7 | 25,8 | 10,0 | **37,5** | 100,0 |
| Psychological Discomfort | 21,7 | 10,0 | **37,5** | 5,0 | 25,8 | 100,0 |
| Physical Disability | 20,8 | 10,0 | **33,3** | 9,2 | 26,7 | 100,0 |
| Psychological Disability | **40,0** | 5,0 | 29,2 | 4,2 | 21,7 | 100,0 |
| Social Disability | **45,8** | 17,5 | 22,5 | 10,0 | 4,2 | 100,0 |
| Handicap | **41,7** | 13,3 | 18,3 | 6,7 | 20,0 | 100,0 |

Figure 3 - Percentage distribution of patients according to the number of dimensions with OHIP

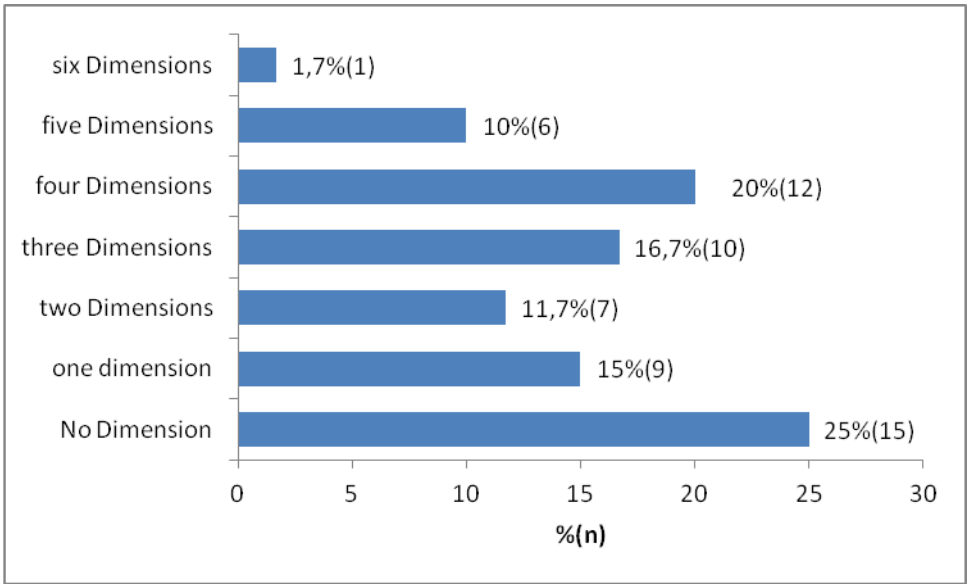

Table 3 - Distribution of patients by gender

| Dimension OHIP | SEX | | | | Total | | p-valor[1] |
|---|---|---|---|---|---|---|---|
| | Male | | Female | | | | |
| | n | % | n | % | n | % | |
| **Functional limitation** | | | | | | | |
| Never or Hardly ever or occasionally | 22 | 51,2 | 21 | 48,8 | 43 | 100,0 | 0,255 |
| Fairly often or Very often | 11 | 64,7 | 6 | 35,3 | 17 | 100,0 | |
| **Physical disability** | | | | | | | |
| Never or Hardly ever or occasionally | 12 | 48,0 | 13 | 52,0 | 25 | 100,0 | 0,255 |
| Fairly often or Very often | 21 | 60,0 | 14 | 40,0 | 35 | 100,0 | |
| **Psychological discomfort** | | | | | | | |
| Never or Hardly ever or occasionally | 16 | 51,6 | 15 | 48,4 | 31 | 100,0 | 0,388 |
| Fairly often or Very often | 17 | 58,6 | 12 | 41,4 | 29 | 100,0 | |
| **Physical pain** | | | | | | | |
| Never or Hardly ever or occasionally | 11 | 39,3 | 17 | 60,7 | 28 | 100,0 | **0,021*** |
| Fairly often or Very often | 22 | 68,8 | 10 | 31,3 | 32 | 100,0 | |
| **Psychological disability** | | | | | | | |
| Never or Hardly ever or occasionally | 19 | 48,7 | 20 | 51,3 | 39 | 100,0 | 0,144 |
| Fairly often or Very often | 14 | 66,7 | 7 | 33,3 | 21 | 100,0 | |
| **Social disability** | | | | | | | |
| Never or Hardly ever or occasionally | 28 | 60,9 | 18 | 39,1 | 46 | 100,0 | 0,089 |
| Fairly often or Very often | 5 | 35,7 | 9 | 64,3 | 14 | 100,0 | |
| **Handicap** | | | | | | | |
| Never or Hardly ever or occasionally | 19 | 55,9 | 15 | 44,1 | 34 | 100,0 | 0,541 |
| Fairly often or Very often | 14 | 53,8 | 12 | 46,2 | 26 | 100,0 | |

* Statistically significant; 1 - Fisher's exact test

Table 4 – Internal consistency between OHIP 14 and its 7 dimensions measured by Cronbach's alpha

| Dimension | Alpha |
|---|---|
| Functional limitation | 0,085 |
| Physical pain | 0,572 |
| Psychological discomfort | 0,469 |
| Physical disability | 0,576 |
| Psychological disability | 0,584 |
| Social disability | 0,650 |
| Handicap | 0,629 |
| **OHIP 14** | **0,761** |

# *CONCLUSÃO*

## CONCLUSÃO

Com base nos resultados deste estudo, foi possível concluir que a infecção pelos herpesvírus HSV -1, EBV e CMV é ubíquota na população estudada e que HSV- 1 pode ser um fator de risco para o agravamento da gravidade da mucosite. Por outro lado, a mucosite oral é um importante efeito colateral agudo que resulta em diminuição da qualidade de vida dos pacientes com câncer.

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# *APÊNDICE*

APÊNDICE I

## TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

**I.Dados de Identificação do Sujeito da Pesquisa ou Responsável Legal**

1.Nome do Paciente:

_____

Documento de Identidade nº: _____ Sexo: M ☐ F ☐

Data nascimento: _____/_____/_____

Endereço: _____nº _____ Apto.: _____

Bairro: _____ Cidade _____Estado _____

CEP: _____-_____ Telefone: (_____) _____

2.Responsável Legal: _____

Natureza (grau de parentesco, tutor, curador, etc.) _____

Documentos de Identidade nº _____Sexo: M ☐ F ☐

Data nascimento: _____/_____/_____

Endereço: _____nº _____ Apto.: _____

Bairro:_____Cidade _____Estado _____

CEP: _____-_____ Telefone: (_____) _____

**II.Dados sobre a Pesquisa Científica**

1.Título do Projeto de Pesquisa: _____

_____

Pesquisador: _____

Cargo/Função: _____Inscrição Conselho Regional nº _____

Pesquisador: _____

## TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Prezado (a) você está sendo convidado(a) a participar como voluntário (a) da presente pesquisa. Após ser esclarecido (a) sobre as informações a seguir, e estiver de acordo em fazer parte da do estudo, registre sua assinatura no final desse documento. Em caso de recusa, não haverá nenhum tipo de penalização ou prejuízo com relação ao tratamento.

**Título da pesquisa: "**Estudos relacionados à etiopatogênese da mucosite e sua repercussão em pacientes com câncer".

**Pesquisador responsável:** Andreza Barkokebas Santos de Faria

**Orientador:** Profº. Dr. Jair Carneiro Leão.

**OBJETIVO:** Identificar se existe relação entre a infecção viral pelos membros da família herpesvirus e a ocorrência e intensidade das mucosites (inflamação das mucosas) orais.

**METODOLOGIA:** Após os pacientes serem submetidos ao exame clínico, as amostras de sangue serão coletadas e armazenadas em temperatura de aproximadamente 5 graus Celsius, sendo posteriormente centrifugadas e o soro separado para análise da presença de anticorpos. As amostras de soro serão avaliadas através do método *Enzyme Linked Immuno Sorbent Assay* (ELISA), utilizando *kits* comerciais da marca *Human GmbH* para o processamento das amostras. As informações clínico-laboratoriais coletadas serão armazenadas em formulário de pesquisa, desenvolvido especificamente para este estudo e as amostras foram processadas no Laboratório Central de Pernambuco (LACEN).Será utilizado um questionário OHIP 14 para avaliar a qualidade de vida dos pacientes com mucosite.

**JUSTIFICATIVA**: A identificação dos Herpesvirus e de sua associação com a mucosite pode permitir o desenvolvimento e/ou aperfeiçoamento de estratégias de tratamento que impliquem menores taxas de complicações e maior qualidade de vida para os pacientes.

**BENEFÍCIOS**: Os participantes e seus familiares receberão orientações de como diagnosticar e prevenir as mucosites, com intuito de promover melhor qualidade da vida. Os pacientes serão submetidos a exame clínico minucioso, sendo avaliadas as condições de saúde bucal. Com o resultado destes exames será orientado de acordo com a necessidade de tratamento individual e encaminhado para as devidas clínicas especializadas.

**RISCOS**: O paciente submetido à pesquisa poderá correr o risco durante o exame clínico, sentir dor ou desconforto devido à punção venosa ou sofrer constrangimentos durante a anamnese, porém a pesquisadora tentará minimizá-los. Todos os materiais utilizados na punção venosa serão descartáveis.

**Eu,_____,RG.Nº. _____Estou ciente de que essas descobertas poderão ser utilizadas no futuro e que talvez meu filho (a) não se beneficie delas, mas outras crianças poderão se beneficiar.Tendo recebido as informações acima, e ciente dos meus direitos, concordo participar desta pesquisa,bem como autorizo toda a documentação necessária, a divulgação e a publicação da mesma, em periódicos científicos, na área da saúde**.

**Tendo ciência do exposto acima, desejo participar da pesquisa.**

Recife, ____ de _____ de _____

_____

Assinatura do paciente (ou responsável)

Assinatura do Pesquisador Assinatura da Testemunha 1 Assinatura da Testemunha 2

**Contato para quaisquer esclarecimentos durante a pesquisa:**
Andreza Barkokebas Santos de Faria
Endereço pesquisador: Rua dos Coelhos, 300 Boa Vista – IMIP ; fone de contato: 2122-4199
Endereço do CEP: Av. da Engenharia s/n 1º andar Cidade Universitária Recife- PE, CEP: 50740-600, fone: 2126-8588

## APÊNDICE II

**FICHA CLÍNICA PARA COLETA DE DADOS**

Nome do paciente: _____

Endereço:_____Bairro_____Cidade_____

Estado_____CEP_____ Fone: ( ) _____

Prontuário: _____

Data de nascimento:_____/____/_____ Sexo: M F

Diagnóstico:_____

Nome dos pais ou responsáveis:_____DN: ____/___/_____

Profissão dos pais ou responsáveis:_____

Endereço (preencher caso seja diferente do paciente):_____

_____Bairro_____Cidade _____Estado_____

**Técnicas:**

**<u>No D0</u>: Coleta de sangue para pesquisa de *HSV-1, Citomegalovírus e Epstein Barr***

( ) Presente ( ) Ausente Se presente: tipo_____

**Classificação da mucosite no 1º dia de observação do pesquisador:**

( ) G0 ( ) GI ( ) GII ( ) GIII ( ) GIV ( ) GV

**Classificação da mucosite no 7º dia a partir do início da terapia anti-neoplásica:**

( ) G0 ( ) GI ( ) GII ( ) GIII ( ) GIV ( ) GV

**Duração da mucosite:**_____ dias **Presença de lesão herpética:** sim ☐ não ☐

| ***Graduação*** | ***Sintomas*** |
|---|---|
| ***Grau 0 (Sem mucosite)*** | *Sem sintomas* |
| ***Grau 1*** | *Eritema da mucosa, ou dor leve. Sintomas respiratórios mínimos, mas não interferem funcionalmente.* |
| ***Grau 2*** | *Eritema doloroso, edema, úlceras ou pseudomembranas, mas o paciente pode se alimentar. Necessidade de dieta modificada. Sintomas respiratórios interferindo funcionalmente.* |
| ***Grau 3*** | *Eritema doloroso, edema, úlceras ou pseudomembranas confluentes. Sangramento ao menor trauma. O paciente não pode se alimentar ou ingerir líquidos adequadamente.* |
| ***Grau 4*** | *Úlceras extensas. Necrose tecidual. Sangramento espontâneo significativo. Necessita de suporte enteral ou parenteral. Risco de vida.* |
| ***Grau 5*** | *Morte* |

Identificação da mucosite oral (segundo NCI, 2007)

**ORAL HEALTH IMPACT PROFILE (OHIP14)**

**FORMULÁRIO PARA A COLETA DE DADOS**

Nome do paciente: _____

Endereço:_____Bairro_____Cidade_____

Estado_____CEP_____ Fone: ( ) _____

Prontuário: _____

Data de nascimento:_____/____/_____ Sexo: M F

Diagnóstico:_____

Nome dos pais ou responsáveis:_____DN: ____/___/_____

Profissão dos pais ou responsáveis:_____

| Dimensões | Nos últimos seis meses, por causa de problemas com seus dentes, sua boca ou dentadura: | Resposta |
|---|---|---|
| Limitação funcional | 1 – Você teve problemas para falar alguma palavra? | |
| | 2 – Você sentiu que o sabor dos alimentos tem piorado? | |
| Dor física | 3 – Você sentiu dores em sua boca ou nos seus dentes? | |
| | 4 – Você se sentiu incomodada ao comer algum alimento? | |
| Desconforto psicológico | 5 – Você ficou preocupada? | |
| | 6 – Você se sentiu estressada? | |
| Inabilidade física | 7 – Sua alimentação ficou prejudicada? | |
| | 8 – Você teve que parar suas refeições? | |
| Inabilidade psicológica | 9 – Você encontrou dificuldade para relaxar? | |
| | 10 – Você se sentiu envergonhado(a)? | |
| Inabilidade social | 11 – Você ficou irritado(a) com outras pessoas? | |
| | 12 – Você teve dificuldade para realizar suas atividades diárias? | |
| Incapacidade | 13 – Você sentiu que a vida, em geral, ficou pior? | |
| | 14 – Você ficou totalmente incapaz de fazer suas atividades diárias? | |

**Opções de respostas: Nunca (0), Raramente (1), Às vezes (2), Repetidamente (3) e Sempre (4)**.

# *ANEXOS*

SERVIÇO PÚBLICO FEDERAL
UNIVERSIDADE FEDERAL DE PERNAMBUCO
Comitê de Ética em Pesquisa

Of. Nº. 299/2011 - CEP/CCS

Recife, 14 de junho de 2011

Registro do SISNEP FR – 408010
CAAE – 0120.0.172.172-11
Registro CEP/CCS/UFPE Nº 148/11
Título: Associação entre herpesvírus HSV1, HSV2, EBV, CMV e mucosite oral em crianças e adolescentes diagnosticados com leucemia linfóide aguda.
Pesquisador Responsável: Andreza Barkokebas Santos de Faria

Senhor (a) Pesquisador (a):

Informamos que o Comitê de Ética em Pesquisa Envolvendo Seres Humanos do Centro de Ciências da Saúde da Universidade Federal de Pernambuco (CEP/CCS/UFPE) registrou e analisou de acordo com a Resolução N.º 196/96 do Conselho Nacional de Saúde, o protocolo de pesquisa em epígrafe, liberando-o para início da coleta de dados em 14 de junho de 2011.

Ressaltamos que a aprovação definitiva do projeto será dada após a entrega do relatório final, conforme as seguintes orientações:

a) Projetos com, no máximo, 06 (seis) meses para conclusão: o pesquisador deverá enviar apenas um relatório final;
b) Projetos com períodos maiores de 06 (seis) meses: o pesquisador deverá enviar relatórios semestrais.

Dessa forma, o ofício de aprovação somente será entregue após a análise do relatório final.

Atenciosamente

Prof. Geraldo Bosco Lindoso Couto
Coordenador do CEP/CCS / UFPE

A
Mestre Andreza Barkokebas Santos de Faria
Programa de Pós-Graduação em Odontologia - CCS/UFPE

Av. da Engenharia, s/n – 1º Andar, Cid. Universitária, CEP 50740-600, Recife - PE, Tel/fax: 81 2126 8588;
www.ufpe.br/ccs; e-mail: cepccs@ufpe.br

SECRETARIA DE SAÚDE DO ESTADO DE PERNAMBUCO - SES
SECRETARIA EXECUTIVA DE VIGILANCIA EM SAÚDE
DIRETORIA GERAL DE LABORATÓRIOS PÚBLICOS-LACEN-PE
NÚCLEO DE ESTUDO E PESQUISA DO LACEN-PE/NEPEL

LACEN - SES - PE

# CARTA DE ANUÊNCIA

Nº. 02/2013

Declaro para os devidos fins, que concordamos com o desenvolvimento do Projeto de Pesquisa intitulado **"Associação entre Herpisvírus HSV1, HSV2, EBV, CMV e Mucosite oral em crianças e adolescentes diagnosticados com Leucemia Linfóide Aguda"** da aluna Andreza Barkokebas Santos de Farias, do curso de Doutorado do Programa de Pós-Graduação Stricto sensu em Odontologia da Universidade Federal de Pernambuco - **UFPE**, sob a orientação do Profº Dr. Jair Carneiro Leão.

Após análise detalhada e criteriosa do presente projeto e considerando a hipótese, os objetivos, a metodologia aplicada e o cronograma, sentimos a falta do detalhamento do orçamento, apesar de constar no sumário;

Considerando o parecer emitido pelo Sr. João Carlos da Silva do setor de virologia do **LACEN-PE**, afirma que o referido projeto pode ser desenvolvido em nossas instalações, desde que, não haja custos financeiros para o **LACEN-PE** e que todos os insumos necessários para o desenvolvimento da pesquisa sejam adquiridos pela pesquisadora, ressaltamos a total isenção do **LACEN-PE**, quanto aos custos financeiros do projeto;

Considerando que o presente projeto foi submetido ao Comitê de Ética em Pesquisa da **UFPE** e obteve autorização para iniciar as coletas de dados em 14 de fevereiro de 2011;

Considerando a **Carta de Anuência** emitida pelo **IMIP**-Instituto de Medicina Integrada Pfº.. Fernando Figueira, em 18 de maio de 2011, assinada pelo Diretor do serviço de Oncologia Pediátrica do **IMIP**, Dr. Francisco Pedrosa;

Entendemos e reconhecemos a real importância do presente projeto pela valiosa contribuição científica que trará para a saúde da população infantil, esclarecendo alguns pontos que até o momento não temos clareza e outros pontos que serão objetos de outras pesquisas estimulando a academia para novos projetos de investigações científicas;

- Ressalto a garantia de solicitar, se necessário, esclarecimentos antes, durante e depois do desenvolvimento da pesquisa e
- No caso do não cumprimento dos itens acima, a liberdade de retirar a minha **ANUÊNCIA** a qualquer momento da pesquisa sem penalidade alguma.

Diante do exposto e não havendo outra consideração a ser feita no momento, somos de **PARECER FAVORÁVEL** que seja pelo **LACEN-PE** oferecida todas as condições necessárias para o profícuo desenvolvimento da pesquisa, esse é o nosso parecer, salvo o melhor juízo.

Recife, 01 de Fevereiro de 2013

Mário Honorato da Silva
Coordenador do NEPEL/LACEN-PE

Mário Honorato da Silva
Coord. do Núcleo de Estudos e Pesquisa
do Lacen - Mat. 266164-1

Rua João Fernandes Vieira, S/N – Boa Vista – Recife/PE – CEP: 50.050-200
Fone: (0xx81) 3181-6406/6407 – Fax: (0xx81) 3181-6146
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Instituto Materno Infantil
Prof. Fernando Figueira
Escola de Pós-graduação em Saúde Materno Infantil
Instituição Civil Filantrópica

IMIP

## CARTA DE ANUÊNCIA

Declaramos para os devido fins, que concordamos em receber ANDREZA BARKOKEBAS SANTOS DE FARIA, doutoranda em Odontologia pela Universidade Federal de Pernambuco, facultando-lhe o desenvolvimento da pesquisa intitulada **"Associação entre herpesvírus HSV1, HSV2, EBV e CMV e mucosite oral em crianças e adolescentes diagnosticados com leucemia linfóide aguda"** no serviço de Oncologia Pediátrica do IMIP.

Informamos ainda, que o serviço atende uma média de 200 (duzentos) novos casos de pacientes com diagnóstico de câncer, por ano, sendo a Leucemia Linfóide Aguda o tipo mais prevalente dentre eles.

Recife, 18 de maio de 2011

Dr. Francisco Pedrosa
Diretor do serviço de Oncologia Pediátrica do IMIP

Dr. Francisco Pedrosa
CRM: 1464

UTILIDADE PÚBLICA MUNICIPAL - Dec. Lei 9851 de 08/11/67
UTILIDADE PÚBLICA ESTADUAL - Dec. Lei 5013 de 14/05/64
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# Journal of Oral Pathology & Medicine

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# Seroprevalence of herpes virus associated with the presence and severity of oral mucositis in children diagnosed with acute lymphoid leukemia

**Andreza Barkokebas Santos de Faria[1], Igor Henrique Moraes Silva[1], Roberta de Godoy Almeida[2], Sirleide Pereira da Silva[3], Alessandra Tavares Carvalho[1], Jair Carneiro Leão[1]**

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**INTRODUCTION: Acute lymphoid leukemia (ALL) is the hematologic neoplasia most commonly diagnosed in children. Among the secondary side effects of chemotherapy, mucositis is the most frequent complication. The aim of this study was to evaluate the seroprevalence of herpes viruses HSV-1, EBV, and CMV and the presence and severity of oral mucositis in children and adolescents diagnosed with ALL.**

**METHODOLOGY: Ninety-two patients diagnosed with ALL were evaluated. Serum samples were collected before chemotherapy and tested by ELISA method. Presence of mucositis was observed on the first day before antineoplastic therapy (D0) and on 7th day post-therapy (D7). Classification of mucositis intensity was performed according to toxicity criteria established by the National Cancer Institute.**

**RESULTS: 70.7% of the patients presented mucositis on the D7, and of these, 60% were classified as Grade I and 40% as Grade II; of the 92 individuals tested, 59 (64.1%) presented antibodies for HSV-1, 57 (62%) for EBV, 75 (81.5%) for CMV_IgG, and 21 (22.8%) for CMV_IgM. Using a logistic regression model, the presence of HSV-1 was observed to be 4.10 times greater in Grade II mucositis severity than in Grade I ($P = 0.03$).**

**CONCLUSION: Based on the findings of this study, it was possible to conclude that infection by the herpes viruses HSV-1, EBV, and CMV is ubiquitous in the studied population and that HSV-1 may be a risk factor for aggravating the severity of mucositis.**

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**Keywords:** acute lymphoid leukemia; herpes virus; mucositis

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## Introduction

Acute lymphoid leukemia (ALL) is the most common hematologic neoplasia in children (1–5), and it represents 75% of all the childhood acute leukemias, and its peak prevalence is in children between 2 and 5 years of age (6). They are primary neoplasias of the bone marrow, characterized by an accumulation of lymphoblasts (undifferentiated cells) to the detriment of mature lymphocytes in the peripheral blood, bone marrow, thymus, and lymph nodes (7).

They are classified according to their histogenesis, primary hematopoietic cell affected (myeloid or lymphoid), and their clinical behavior (acute or chronic) (8–10). The frequency of incidence in the population from 0 to 14 years is 1/25 000 individuals/year, and the risk of developing the disease in the first 10 years is 1/2880. ALL is more common in white children than in Afro-descendant/black children (1,8:1) and in boys than in girls (1,2:1) (8, 11).

The etiology has not yet been determined, although the following have been emphasized as possible causes: effects of irradiation, exposure to antineoplastic drugs, associated genetic and immunologic factors, and exposure to some viruses (12–15). Due to the immunosuppression caused by antineoplastic therapy, some clinical complications are expected in children submitted to chemotherapy during treatment (16).

Among the secondary side effects of chemotherapy, mucositis is the most common complication of the cytotoxicity caused by chemotherapy (17–30), and its estimated prevalence is between 30% and 75% (31).

Oral mucositis results from the direct inhibitory effect of the chemotherapy drugs on mucosal cell replication and proliferation, which promotes a reduction in the capacity of renovation of the basal layer of the epithelium. These events favor atrophy of the mucosa, accentuated reduction in collagen production, and eventual ulceration (32). The release of substances in the conjunctive tissue, which exacerbate the inflammatory response, added to the epithelial alterations, complete the pathogenesis of mucositis,

which is characterized by five stages: onset, regulation, amplification, ulceration, and healing (33).

The toxic effects of chemotherapy on the oral mucosa being soon after its administration, attaining peak intensity between the 7th and 10th day after beginning with the chemotherapy cycle, with resolution occurring in <2 weeks (34).

In patients with acute lymphoid leukemia (ALL), this secondary effect is related to a frequency ranging from 18 to 33% (35–37). The immunosuppression secondary to chemotherapy treatment favors the occurrence of infections by opportunist agents, such as fungi and high seroprevalence of herpes viruses (17, 21, 38–40), resulting in diminished quality of life of the irradiated patient (41, 42).

Oral infections by herpes viruses are very common, with emphasis on HSV-1, which is manifested as a necrotizing ulcerative lesion in approximately 40–70% of the patients (43). Its occurrence represents a significant risk factor for systemic infections, particularly in neutropenic patients (44, 45).

The purpose of this study was to evaluate the seroprevalence of herpes viruses HSV-1, EBV, and CMV and the presence and severity of oral mucositis in children and adolescents diagnosed with ALL.

## Methodology

A cross-sectional study was conducted and was approved by the Research Ethics Committee CEP/CCS/UFPE N.148/2011 with SISNEP FR – 408010 registrations. The participants in the research signed a Term of Free and Informed Consent; they were examined, and their data were filled out on a Clinical Record Chart. A total of 92 patients diagnosed with acute lymphoid leukemia were evaluated; they had not undergone previous treatment and were consecutively admitted to the Pediatric Oncology Service of the 'Instituto de Medicinal Integral Prof. Fernando Figueira (IMIP)', in the period from August 2011 to September 2012. For sample calculation, the EpiInfo program was used, and an error of 6% was adopted.

All the patients with the diagnosis of ALL were followed up by the oncologist doctors and by the researcher responsible for the study. During the period of hospitalization, the patients included in the study were evaluated with the aim of identifying and classifying the episodes of oral mucositis. All children underwent chemotherapy sessions with very similar protocols using methotrexate as the primary drug, however, aspects including body weight and general state of health were also considered.

The Kappa test of agreement and the intra- and inter-observer integrity were performed for two dental residents, who were being monitored by an experienced dentist belonging to the service. This process took place during sessions of discussion lasting 2 h and training for 3 days ($k = 0.79$). Evaluations with regard to the presence of mucositis were performed on D0 pf antineoplastic therapy and on D7. Classification of the intensity of mucositis was performed in accordance with the toxicity criteria established by the National Cancer Institute (NCI), version 3.0 (46), in which five Grades are defined, and briefly summarized in Table 1.

**Table 1** Classification of mucositis, in accordance with the NCI, 2006

| *Grading* | *Symptoms* |
|---|---|
| Grade 0 (Without mucositis) | Without symptoms |
| Grade 1 | Erythema of the mucosa, or slight pain. Minimal respiratory symptoms, but they do not interfere functionally |
| Grade 2 | Painful erythema, edema, ulcers or pseudomembranes, but the patient is able to eat. Need for modified diet. Respiratory symptoms interfering functionally |
| Grade 3 | Painful Erythema, edema, ulcers or confluent pseudomembranes. Bleeding with the slightest trauma. The patient is unable to eat or swallow liquids adequately |
| Grade 4 | Extensive ulcers. Tissue necrosis. Significant spontaneous bleeding. Needs enteral or parenteral support. Life-threatening Risk |
| Grade 5 | Death |

Reference: National Cancer Institute (46).

*Collection of material for identification of herpes viruses*

Approximately 10 ml of total blood was collected from the participants, in tubes containing EDTA. The blood samples collected before chemotherapy were stored at a temperature of approximately five degrees Celsius, for a maximum of 48 h. Afterward, these were centrifuged, and the serum was separated and analyzed for the presence of antibodies. The serum samples were evaluated by means of the *enzyme linked immuno sorbent assay* (ELISA) method, using commercial kits of the *Human GmbH* brand, for processing the samples. The IgM and IgG antibodies were tested for CMV and IgG antibodies to HSV and EBV, once the latter frequently have characteristic clinical signs of acute infection.

The clinical-laboratory information collected was stored on the research form, specifically developed for this study, and the samples were processed in the Central Laboratory of Pernambuco ('Laboratório Central de Pernambuco – LACEN').

*Data analysis*

For inferential statistical analysis of the variables *herpes viruses* and the *presence of mucositis*, the Pearson's chi-square test was used, and the level of significance of 5% was adopted. A multivariate analysis was performed, using the binary logistic regression model to evaluate the association between the degrees of severity of mucositis and herpes viruses. Hosmer–Lemeshow statistics were used to verify the quality of adjustment of the model. The data were typed into an Excel spreadsheet, and the software program used to obtain the statistical calculation was SPSS (Statistical Package for Social Sciences) version 17.0 (IBM Corporation, Armonk, NY, USA).

## Results

Ninety-two patients were followed up during the research, with 53.3% being of the male sex and 46.7% of the female sex, with the median age of 6 years, ranging between 2 and 10 years.

Around 65 (70.7%) of the patients presented mucositis on the 7th day, and of these, 39 (60%) were classified as Grade I and 26 (40%) as Grade II; of the 92 individuals tested, 59 (64.1%) presented antibodies for HSV-1, 57 (62%) for EBV, 75 (81.5%) for CMV_IgG, and 21 (22.8%) for CMV_IgM; around 9.8% presented concomitant seroprevalence positive for three types of viruses; 56.5% presented HSV-1 and CMV_IgG together, as shown in Table 2.

As regards the prevalence of herpes viruses due to the presence of mucositis, it may be emphasized that there was a higher percentage, 85.7%, of CMV_IgM and HSV-1+CMV_IgM viruses which together presented mucositis, however, in no combination of viruses was there statistically significant difference, as shown in Table 3.

Of the 92 patients in the sample, 89 (96.7%) presented at least one type of virus, as may be observed in Table 4, which correlates the quantity of viruses per patient in relation to the presence of mucositis. The 3 (3.3%) patients who did not present any type of virus, presented Grade I mucositis on the 7th day. However, there was no statistically significant difference between the presence of mucositis in comparison with the quantity of viruses present in the studied population.

A multivariate analysis was performed using a binary logistic regression model. Hosmer–Lemeshow statistics were used to verify the quality of adjustment of the model. The Wald test verified the significance if each variable individually, and in the model in the present research, two variables were significant, as shown in Table 5.

The variable considered a risk factor for the severity of mucositis, in the multivariate logistic regression analysis, was the virus HSV-1 (OR = 4.102; IC: 1.149–14.651; $P = 0.03$), and as a protective variable, the virus CMV (OR = 0.248; IC: 0.062–0.9991; $P = 0.049$) that is to say: in the logistic model, the presence of HSV-1 was 4.10 times greater in Grade II severity of mucositis than in Grade I ($P = 0.03$), and there were 75.2% chances of the presence of CMV not occurring in the group with Grade II type of severity ($P = 0.049$).

**Table 2** Description of gender, presence of mucositis, mucositis grading, and presence of herpes virus

| *Variables* | n | % |
|---|---|---|
| Sex | | |
| Male | 49 | 53.3 |
| Female | 43 | 46.7 |
| Presence of mucositis on 7th day ($n = 92$) | 65 | 70.7 |
| Classification of mucositis on 7th day | ($n = 65$) | |
| I | 39 | 60.0 |
| II | 26 | 40.0 |
| Types of herpes virus ($N = 92$) | | |
| HSV-1 | 59 | 64.1 |
| EBV | 57 | 62.0 |
| CMV_IgG | 75 | 81.5 |
| CMV _IgM | 21 | 22.8 |
| HSV1+EBV | 41 | 44.6 |
| HSV1+CMV_IgG | 52 | 56.5 |
| HSV1+CMV_IgM | 14 | 15.2 |
| EBV+CMV_IgG | 47 | 51.1 |
| EBV+CMV_IgM | 14 | 15.2 |
| HSV1+EBV+CMV_IgG | 37 | 40.2 |
| HSV1+EBV+CMV_IgM | 10 | 10.9 |
| EBV+CMV_IgG+CMV_IgM | 12 | 13.0 |
| HSV1+CVM_IgG+CVM_IgM | 13 | 14.1 |
| HSV1+EBV+CMV_IgG+CMV_IgM | 9 | 9.8 |

**Table 3** Correlation between the occurrence of oral mucositis and the presence of herpes virus in pediatric patients with leukemia

| | *Presence of mucositis on 7th day* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *No* | | *Yes* | | *Full* | | |
| *Herpes virus* | n | % | n | % | n | % | *P-value** |
| HSV-1 | 18 | 30.5 | 41 | 69.5 | 59 | 100 | 0.469 |
| EBV | 16 | 28.1 | 41 | 71.9 | 57 | 100 | 0.454 |
| CMV_IgG | 24 | 32.0 | 51 | 68.0 | 75 | 100 | 0.192 |
| CMV _IgM | 3 | 14.3 | 18 | 85.7 | 21 | 100 | 0.069 |
| HSV1+EBV | 12 | 29.3 | 29 | 70.7 | 41 | 100 | 0.586 |
| HSV1+CMV_IgG | 17 | 32.7 | 35 | 67.3 | 52 | 100 | 0.285 |
| HSV1+CMV_IgM | 2 | 14.3 | 12 | 85.7 | 14 | 100 | 0.152 |
| EBV+CMV_IgG | 13 | 27.7 | 34 | 72.3 | 47 | 100 | 0.446 |
| EBV+CMV_IgM | 3 | 21.4 | 11 | 78.6 | 14 | 100 | 0.360 |
| HSV1+EBV+CMV_IgG | 11 | 29.7 | 26 | 70.3 | 37 | 100 | 0.564 |
| HSV1+EBV+CMV_IgM | 2 | 20.0 | 8 | 80.0 | 10 | 100 | 0.390 |
| EBV+CMV_IgG+ CMV_IgM | 3 | 25.0 | 9 | 75.0 | 12 | 100 | 0.509 |
| HSV1+CVM_IgG+ CVM_IgM | 2 | 15.4 | 11 | 84.6 | 13 | 100 | 0.197 |
| HSV1+EBV+CMV_IgG+ CMV_IgM | 2 | 22.2 | 7 | 77.8 | 9 | 100 | 0.475 |

*P*-value = value obtained by chi-square test with 5% significance.

**Table 4** Correlation between the presence of oral mucositis and the number detected by herpes virus patients with childhood leukemia

| | *Presence of mucositis on 7th day* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *No* | | *Yes* | | *Total* | | |
| *Number of virus present per patient* | n | % | n | % | n | % | *P-value** |
| 1 | 7 | 25.9 | 13 | 21.0 | 20 | 22.5 | 0.873 |
| 2 | 8 | 29.6 | 16 | 25.8 | 24 | 27.0 | |
| 3 | 10 | 37.0 | 26 | 41.9 | 36 | 40.4 | |
| 4 | 2 | 7.4 | 7 | 11.3 | 9 | 10.1 | |
| Full | 27 | 100.0 | 62 | 100.0 | 89 | 100.0 | |

*P*-value = value obtained by chi-square test with 5% significance.

## Discussion

Although seroepidemiological studies have pointed out that over 90% of the world population have serum antibodies against at least one of the strains of HSV (47), only 40% of these individuals have sensitivity for the development of secondary herpetic manifestations (48). For Wade et al. (1989), up to 60% of the individuals with serology positive for HSV present asymptomatic or oligosymptomatic conditions not recognized by the patients themselves (49).

Previous studies by Elad et al. (2010) have proposed recommendations based on evidences for the prevention and treatment for oral viral infections in patients with cancer. The available studies mainly refer to the infections by HSV-1, and to a lesser extent, to other members of the Herpesviridae family.

Table 5 Final model of logistic regression on the severity II in severity considering herpes viruses HSV-1 and EBV CMV_IgG as explanatory variables

| | | | | | | | IC 95% para OR | |
|---|---|---|---|---|---|---|---|---|
| | *B* | *SE* | *Wald* | *df* | *P-value* | *OR (Razão de Chances)* | *LowerLimit* | *Upper Limit* |
| HSV1 | 1.41 | 0.65 | 4.72 | 11 | 0.030 | 4.102 | 1.149 | 14.651 |
| CMV_IgG | −1.39 | 0.71 | 3.84 | 11 | 0.049 | 0.248 | 0.062 | 0.999 |
| EBV | 0.08 | 0.58 | 0.02 | 11 | 0.885 | 1.087 | 0.349 | 3.390 |
| Constant | −0.32 | 0.67 | 0.22 | 11 | 0.636 | 0.730 | | |
| Adjustment model[a] | 0.495 | | | | | | | |

[a]Adjustment model by Hosmer-Lemeshow.

The relations between viral infectious diseases and ALL continue to be a question of interest and speculation. The results of serological tests in the studies of Djuric et al. (2009) have shown that 91.7% of the individuals were seropositive for HSV-1. In addition, the studies of Tesse et al. (2009) have affirmed that the seroprevalence of IgG antibodies for HSV and CMV in leukemic children was significantly higher than it was in the controls. A similar observation was made by Loutfy et al. (2006) in Egyptian children, although their results were not statistically significant. These findings corroborate the results of the present research with regard to the high seroprevalence of HSV, and particularly of CMV in the studied population.

Shlehofer et al. (1996) also added that the seroprevalence of IgG EBV antibodies tends to be greater in children with ALL than in healthy individuals, and in our findings, the prevalence of EBV was considered high and practically the same as that of HSV. There is strong correlation between latent infection by EBV – responsible for infectious mononucleosis in humans – and the development of different malignant tumors, such as Burkitt's lymphoma, Hodgkin's disease, Lymphoma B, and nasopharyngeal carcinoma. Proteins expressed by EBV act directly as oncogenes, stimulating proliferation of the infected cells. In spite of no description in the literature correlating the presence of this virus with the aggravation of chemotherapy-induced oral mucositis, its participation as co-factor in immunosuppressed patients has not been discarded (50).

Whereas, the studies of Lalla et al. (2008) and Nicolatou-Galitis et al. (2006) have related to a positive correlation between the occurrence of severe oral mucositis and the presence of HSV 1. These findings are in alignment with the results of the present research, which demonstrated that infection by HSV was a risk factor for aggravation of the severity of mucositis, as the presence of HSV-1 was 4.10 times greater in Grade II than in Grade I mucositis and was shown to be statistically significant by means of a logistic regression model.

However, Redding et al. (1998) obtained no correspondence between the presence of the HSV 1 virus and the degrees of severity of oral mucositis, in addition to not obtaining a satisfactory response to the use of antiviral agents in the studied populations.

An explanation for the discrepancy of these findings may be found in the population of patients involved. The majority of studies that refer to HSV 1 as a cofactor in the aggravation of mucositis lesions involve patients submitted to schemes of chemotherapy that include immunosuppressive drugs, with the possible appearance of neutropenia.

Moreover, it has been suggested that it is possible that HSV might have behaved as a risk factor due to the fact that its latency occurs in the sacral and trigeminal ganglia, which may serve as epicenter in the clinical recurrences, thus aggravating the degree of mucositis. Therefore, HSV-1 could modulate the immune response and collaborate in triggering more complicated clinical problems than those observed in immunocompetent individuals (51). Whereas, the latency of CMV occurs in the cells of salivary glands, endothelium, and in macrophages, and in spite of having presented a higher prevalence, it did not contribute to the aggravation of mucositis, however, its participation as a possible cofactor responsible for this has not been discarded.

With regard to the toxic effects of chemotherapy on the oral mucosa, studies have related that they begin soon after administration of this therapy, attaining a peak intensity between the 7th and 10th day after beginning the chemotherapy cycle, with resolution occurring in <2 weeks (34, 43), this finding confirms the present study, in which 70,7% of the studied population presented mucositis on the 7th day post-antineoplastic therapy, and reiterated by the studies of Djuric et al. (2009) who demonstrated that 60% of the patients with ALL developed mucositis. These results are in agreement with the previous studies of Djuric et al. (2006), who reported the presence of mucositis in around 58–64% of the studied patients, and are aligned with the findings of CHAN et al. (2003), who related that 12.8% of the patients presented mucositis on day 1, 58.5% on day 8, and 42.5% on 16 days of chemotherapy. Furthermore, Bonan et al. (2005) and Trotti et al. (2003) added that for the majority of patients, 10–14 days are sufficient for repairing the lesioned tissue.

Based on the findings of this study, it was possible to conclude that infection by the herpes viruses HSV-1, EBV, and CMV is ubiquitous in the studied population and that HSV-1 may be a risk factor for aggravating the severity of mucositis.

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## Conflict of interest

The authors declare that there was no conflict of interests.