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MUCOSITE ORAL EM PACIENTES ONCOLÓGICOS PEDIÁTRICOS: OCORRÊNCIA, ESCALAS DE MENSURAÇÃO, TEMPO DE HOSPITALIZAÇÃO E FATORES ASSOCIADOS

FABIO GOMES DOS SANTOS

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ORAL MUCOSITIS IN PEDIATRIC ONCOLOGICAL PATIENTS: OCCURRENCE, MEASUREMENT SCALES, LENGTH OF HOSPITALIZATION AND ASSOCIATED FACTORS

Tese apresentada ao Programa de Pós-Graduação em Odontologia, da Universidade Federal da Paraíba, como parte dos requisitos para obtenção do título de Doutor em Odontologia – Área de Concentração Ciências Odontológicas.

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“Posso não concordar com nenhuma das palavras que você disser, mas defenderei até a morte o direito de você dizê-las”. (Voltaire / Evelyn Beatrice Hall)

RESUMO

O câncer infantojuvenil é a segunda maior causa de morte nessa população. Apesar do avanço do tratamento oncológico, as terapias antineoplásicas promovem efeitos adversos aos tecidos sadios, trazendo prejuízos anatômicos e funcionais aos pacientes. A mucosite oral (MO) é o efeito adverso mais comum e sua prevalência pode chegar a 90% na forma leve/moderada e 35% na forma mais grave, sendo maior em crianças e adolescentes em relação aos adultos. Existem vários instrumentos utilizados para avaliação da MO, no entanto, poucos são destinados à população infantojuvenil. A ocorrência de MO tem sido associada, de acordo com a literatura, a fatores inerentes aos indivíduos e ao regime terapêutico. O objetivo geral deste estudo foi aprofundar o conhecimento sobre a MO em crianças e adolescentes com câncer em tratamento quimioterápico, por meio da identificação da ocorrência da MO, suas escalas de mensuração, o impacto deste agravo no tempo de hospitalização e fatores associados em pacientes oncológicos pediátricos. Para isso, o presente estudo foi dividido em quatro artigos científicos. No artigo 1, por meio de uma série de casos, foram reportados 9 casos de pacientes oncopediátricos com leucemia, que foram acompanhados por 10 semanas consecutivas e apresentaram mucosite oral grave (MOG) já na primeira semana de tratamento. Os pacientes tiveram em média 4,0 e 5,5 episódios de MO e MOG, respectivamente. A saliva e os lábios foram os itens mais afetados. No artigo 2, realizou-se uma revisão sistemática de acordo com o *checklist* PRISMA e SWIM, registrada na PROSPERO, para verificar se a severidade da MO influencia no tempo de hospitalização de pacientes oncopediátricos. Três estudos foram elegíveis para a síntese qualitativa. Todos os estudos apresentaram baixo risco de viés nos domínios avaliados por meio da escala Newcastle-Ottawa. Um estudo verificou um aumento de 4,6 dias de hospitalização para cada aumento em uma unidade da escala da Organização Mundial de Saúde (OMS) para MO. Os demais estudos também observaram que os pacientes com escores mais graves requereram maior tempo de hospitalização. No artigo 3, foi escrita uma *short communication* acerca dos instrumentos utilizados para avaliar a condição oral de pacientes pediátricos em tratamento antineoplásico. Os principais instrumentos para este propósito são as escalas da OMS, da *National Cancer Institute - Common Terminology Criteria for Adverse Events* (NCI-CTCAE), e o *Oral Assessment Guide*

(OAG). Todos são capazes de identificar e graduar as ulcerações, no entanto o OAG se destaca por avaliar os critérios que podem estar associados ao risco de ocorrência da MO. No artigo 4, por meio de uma coorte prospectiva de curta duração, foram avaliados fatores de risco associados à ocorrência da MO. A incidência variou entre 50,5% e 64,8% e 16,2% a 31,4% para a MO e MOG, respectivamente. O número de semanas com MO e MOG foram 7,6 e 2,4; respectivamente. A saliva e os lábios foram os itens mais acometidos com os escores 2 e 3. Apenas o tempo desde a última sessão de quimioterapia está associado ao aparecimento dessas lesões e ao escore OAG. Diante do exposto, conclui-se que apesar de não haver uma escala padrão para avaliar a MO, o OAG é uma excelente opção para mensurar essa complicação em crianças e adolescentes visto sua análise não ser centrada no diagnóstico de úlcera e, assim, permitir verificar outros aspectos que podem influenciar na ocorrência da MO. Além disso, a literatura necessita de estudos que proporcionem melhor evidência sobre os fatores de risco da MO e MOG e o impacto da MO no tempo de hospitalização de pacientes oncológicos pediátricos. Contudo, quanto maior o tempo desde a última sessão de quimioterapia menor o risco de ocorrência e severidade da MO.

Palavras-chave: Mucosite oral; Quimioterapia; Criança; Adolescente; Câncer.

ABSTRACT

Childhood cancer is the second leading cause of death in this population. Despite advances in oncological treatment, antineoplastic therapies have adverse effects on healthy tissues, causing anatomical and functional damage to patients. Oral mucositis (OM) is the most common adverse effect and its prevalence can reach 90% in the mild/moderate form and 35% in the most severe form, being higher in children and adolescents compared to adults. There are several instruments used to assess WM, however, few are intended for children and adolescents. The occurrence of OM has been associated, according to the literature, with factors inherent to individuals and the therapeutic regimen. The general objective of this study was to deepen the knowledge about OM in children and adolescents with cancer undergoing chemotherapy, by identifying the occurrence of OM, its measurement scales, the impact of this condition on the length of hospitalization, and associated factors in cancer patients. pediatric. For this, the present study was divided into four scientific articles. In article 1, through a series of cases, 9 cases of oncopediatric patients with leukemia were reported, who were followed up for 10 consecutive weeks and presented with severe oral mucositis (MOG) in the first week of treatment. Patients averaged 4.0 and 5.5 episodes of MO and MOG, respectively. Saliva and lips were the most affected items. In article 2, a systematic review was carried out according to the PRISMA and SWIM checklist, registered in PROSPERO, to verify whether the severity of OM influences the length of hospitalization of oncopediatric patients. Three studies were eligible for qualitative synthesis. All studies showed a low risk of bias in the domains assessed using the Newcastle-Ottawa scale. One study verified an increase of 4.6 days of hospitalization for each increase in one unit of the World Health Organization (WHO) scale for OM. The other studies also observed that patients with more severe scores required longer hospital stays. In article 3, a short communication was written about the instruments used to assess the oral condition of pediatric patients undergoing antineoplastic treatment. The main instruments for this purpose are the WHO scales, the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), and the Oral Assessment Guide (OAG). All are capable of identifying and grading ulcerations, however, OAG stands out for evaluating the criteria that may be associated with the risk of occurrence of OM. In article 4, through

a short-term prospective cohort, risk factors associated with the occurrence of OM were evaluated. The incidence varied between 50.5% and 64.8% and 16.2% and 31.4% for MO and MOG, respectively. The number of weeks with MO and MOG were 7.6 and 2.4; respectively. Saliva and lips were the most affected items with scores 2 and 3. Only the time since the last chemotherapy session is associated with the appearance of these lesions and the OAG score. In view of the above, it is concluded that although there is no standard scale to assess WM, the OAG is an excellent option to measure this complication in children and adolescents, since its analysis is not centered on the diagnosis of ulcers and, therefore, allows for the verification of other aspects that may influence the occurrence of OM. In addition, the literature needs studies that provide better evidence on the risk factors for OM and OMG and the impact of OM on the length of hospitalization of pediatric cancer patients. However, the longer the time since the last chemotherapy session, the lower the risk of OM occurrence and severity.

Keywords: Oral mucositis; Chemotherapy; Child; Adolescent; Cancer.

SUMÁRIO

1 INTRODUÇÃO

O câncer em crianças e adolescentes representa 1% de todas as neoplasias malignas diagnosticadas anualmente no mundo (Bhakta et al., 2019). No entanto, é uma doença que, para esses indivíduos de zero a 19 anos, não pode ser prevenida e corresponde à segunda maior causa de morte em muitos países, especialmente nos mais desenvolvidos (WHO, 2021; PAHO, 2022; Wu et al., 2022). A incidência, sobrevida e mortalidade do câncer infantojuvenil nos países de média e baixa renda têm sido insuficientemente documentadas (Bhakta et al., 2019). Porém, a taxa de sobrevivência nesses países varia entre 20 e 30% (WHO, 2021).

Devido ao avanço no tratamento do câncer por meio da quimioterapia (QT), radioterapia (RT), cirurgia ou a combinação dessas modalidades, a chance de cura é de aproximadamente 80% para crianças e adolescentes que têm acesso aos serviços de saúde (PAHO, 2022; WHO, 2021). Contudo, o efeito citotóxico da QT e RT nas células malignas também promove efeitos adversos aos tecidos sadios, trazendo prejuízos anatômicos e funcionais aos pacientes (Sonis et al., 2004; Raber-Durlacher, Elad, Barasch, 2010; Docimo, Anastasio, Bensi, 2022).

As complicações orais das terapias não cirúrgicas para o câncer incluem danos às mucosas, às glândulas salivares, aos dentes, manifestações musculoesqueléticas e distúrbios sensoriais (Elad, Zadik, Yarom, 2017). Muitas delas são comuns e dolorosas, impactando negativamente na qualidade de vida dos pacientes e no custo do manejo dessas complicações (Sonis, 2022).

A mucosite oral (MO) é um efeito adverso comum e significativo resultante da QT, RT e do transplante de células-tronco hematopoiéticas (TCTH), sendo a prevalência variável de acordo com o regime quimioterápico e o tipo de tratamento instituído (Rubenstein et al., 2004; Miranda-Silva et al., 2021). Em crianças e adolescentes em tratamento quimioterápico, a prevalência da MO pode chegar a 90% na forma leve/moderada e 35% na forma mais grave (Docimo, Anastasio, Bensi, 2022), sendo mais frequente nessa faixa etária em comparação aos adultos devido à maior taxa de proliferação celular (Otmani, Hattad; 2021).

A epidemiologia da MO é controversa, pois muitas vezes só é registrada quando o paciente apresenta uma lesão severa, que requer algum cuidado clínico e, além disso, não existe uma escala padrão para avaliar a sua severidade (Pulito et al., 2020). Os instrumentos utilizados para graduar a MO baseiam-se em critérios

estritamente clínicos, outros apenas funcionais ou por meio de relatos dos pacientes, dificultando a comparabilidade entre eles, especialmente em casos leves ou moderados (Sonis et al., 2022).

Clinicamente, a MO inicia-se por um eritema doloroso, podendo evoluir para descamação e ulceração do tecido, o que favorece a entrada de microrganismos (Cheng, Chang, Yuen, 2004; Shetty et al., 2022). Além da dor provocada pela lesão, os pacientes podem apresentar dificuldade para falar, engolir e mastigar, necessitando de suporte nutricional, medicamentos para controle da dor ou infecções. Com isso, a MO pode aumentar o tempo de internação e gastos hospitalares e modificar ou interromper o tratamento oncológico (Cheng, Chang, Yuen, 2004; Mazhari, Shirazi, Shabzendehdar, 2019; Otmani, Hattad, 2021; Elad et al., 2022; Docimo, Anastasio, Bensi, 2022).

O risco de ocorrência da MO em crianças e adolescentes tem sido relacionado ao tipo de tratamento (QT e/ou RT), ao regime terapêutico (medicamento, dose, frequência de administração), fatores relacionados ao paciente (características sociodemográficas, fatores genéticos e epigenéticos, parâmetros sistêmicos de saúde, condição de saúde oral) e fatores relacionados ao tumor (Farias-Gabriel et al., 2021; Sonis et al., 2022).

Desde 2011, nosso grupo de pesquisa tem avaliado a condição oral de crianças e adolescentes com câncer assistidos no Hospital Napoleão Laureano. A partir disso, o grupo tem se destacado internacionalmente por meio de publicações que abordam a prevenção e o tratamento da MO; o acesso e satisfação dos pacientes oncopediátricos quanto à saúde bucal; monitoramento da cavidade oral durante o tratamento oncológico; qualidade de vida dos pacientes oncopediátricos; aspectos clínicos, hematológicos e epigenéticos associados à ocorrência da MO; e o impacto da Covid-19 no atendimento odontológico para pacientes oncopediátricos.

A partir desses achados, a pergunta norteadora para a elaboração dos artigos desta tese foi: a MO e a MOG apresentam os mesmos fatores de risco? Baseado no exposto, o objetivo geral deste estudo foi ampliar o conhecimento sobre a MO em crianças e adolescentes em tratamento quimioterápico, por meio da: (1) identificação da ocorrência da MO, (2) verificação das escalas de mensuração da MO em crianças e adolescentes, (3) avaliação do impacto deste agravo no tempo de hospitalização e (4) identificação de fatores associados a sua ocorrência na população pediátrica.

2 REVISÃO DA LITERATURA

Neste capítulo, serão abordados alguns conceitos, dados epidemiológicos, aspectos clínicos, complicações e manejo do tratamento oncológico em crianças e adolescentes.

2.1 Epidemiologia do câncer infantojuvenil

A maioria dos cânceres em crianças e adolescentes possuem causa desconhecida, mas a literatura já tem atribuído que aproximadamente 10% deles são causados por fatores genéticos (WHO, 2021). As leucemias, tumores cerebrais, linfomas, sarcomas e lesões malignas de células germinativas são mais prevalentes em crianças abaixo de 15 anos, enquanto o neuroblastoma, nefrobastoma e retinoblastoma acometem geralmente crianças mais novas (Lam et al., 2019). Nos adolescentes, o câncer de tireoide, linfoma de Hodgkin, câncer de cérebro e outros cânceres do sistema nervoso são os mais prevalentes (Miller et al., 2020).

Em um contexto global, a leucemia é a neoplasia mais frequente e fatal em crianças e adolescentes de ambos os sexos (Wu et al., 2022). No Brasil, a epidemiologia do câncer infantojuvenil segue o padrão mundial, em que o grupo das leucemias, doenças mieloproliferativas e mielodisplásicas representam cerca de 30% dos casos (Lucena et al., 2022).

A estimativa do câncer infantojuvenil para o Brasil no triênio 2020-2022 é de 8.460 por ano, sendo maior para o sexo masculino e maior risco na região sul, seguida do sudeste, centro-oeste, nordeste e norte (INCA, 2020). No cenário regional e local, os tumores sólidos correspondem a 56,9% dos casos no Nordeste e 57,3% na Paraíba (Lucena et al., 2022; Silva et al., 2022).

2.2 Complicações orais decorrentes do tratamento do câncer infantojuvenil

As principais modalidades de tratamento do câncer são a quimioterapia, radioterapia, cirurgia ou a combinação delas (OMS, 2021). O avanço do tratamento oncológico nos últimos anos aumentou significativamente a sobrevida dos pacientes oncopediátricos (PAHO, 2022), contudo, eles podem ocasionar efeitos

adversos agudos ou tardios nos pacientes (Allen, Logan, Gue, 2010; King, 2019; Ritwik, Chrisentery-Singleton, 2020).

Os pacientes submetidos à radioterapia na região de cabeça e pescoço apresentam mais alterações dentárias e maxilofaciais do que os pacientes que realizam apenas quimioterapia (Jaffe et al., 1984; King 2019).

Dentre as complicações orais agudas decorrentes do tratamento oncológico em crianças estão a MO, infecções por candida e herpes simples, ressecamento labial, xerostomia/hipossalivação, dor neuropática, gengivite e cárie (Allen, Logan, Gue, 2010; Ritwik, Chrisentery-Singleton, 2020).

Nas crianças, os efeitos tardios da quimioterapia (combinada ou não à radioterapia) estão associados ao aumento do risco de agenesia, descoloração, retenção prolongada, hipoplasia do esmalte, microdontia, apicificação prematura e diminuição da taxa de fluxo salivar e maior experiência de cárie (Busenhart et al., 2018; King 2019; Seremidi et al., 2021).

Já os efeitos tardios da radioterapia na cavidade oral incluem, além dos efeitos observados na quimioterapia, retardo/falha no desenvolvimento e neoformação óssea, xerostomia/hipossalivação, trismo, alteração no paladar, necrose dos tecidos moles e deformidades faciais (King, 2019).

Esses efeitos podem resultar em impactos funcionais, psicológicos e econômicos, sendo necessária a adoção de medidas preventivas e curativas (Busenhart et al., 2018).

Dentre os efeitos adversos, a MO destaca-se como o mais comum nos pacientes submetidos à QT, RT e ao transplante de células-tronco hematopoiéticas (TCTH) (Rubenstein et al., 2004; Miranda-Silva et al., 2021).

2.3 Fisiopatologia e apresentação clínica da mucosite oral

A MO é resultado de uma sequência de eventos biológicos interrelacionados que tem como consequência a injúria tecidual a partir da QT ou RT, descrito em um modelo de 5 fases: iniciação, regulação e geração de mensagens, sinalização e amplificação, ulceração e cicatrização (Villa, Sonis, 2020).

A fase de iniciação começa imediatamente após a administração da QT ou RT e a cascata de eventos é ativada a cada dose. No entanto, o dano direto inicial nas

células basais do epitélio e da submucosa não é suficiente para provocar uma lesão oral clinicamente extensa (Sonis, 2007).

Embora as vias de ativação sejam estimuladas em segundos do início do tratamento, existe um intervalo entre os danos celular e a manifestação clínica da lesão (Figura 1) (Lalla et al., 2019).

Na segunda fase, ocorre a síntese da ceramida e a ativação dos fatores de transcrição p53, NF-Kb e NRF2 responsáveis pela apoptose das células bem como pela produção de citocinas pró-inflamatórias (TNF- α, IL-1 β e IL-6) que exacerbam os danos no epitélio, tecido conjuntivo e endotélio (Shetty et al., 2022).

A geração e ativação de diversas vias durante as duas primeiras fases levam à amplificação e potencialização dos sinais moleculares e celulares por meio de *feedback* positivos repetidos, aumentando a lesão tecidual e prolongando os danos por dias após o início do tratamento quimio-radioterápico (Sonis, 2007).

O paciente em tratamento quimioterápico pode apresentar a mucosite oral grave (MOG) durante três a cinco semanas (Villas, Sonis, 2015; Sonis, 2022). Enquanto na RT, devido ao acúmulo de radiação, as úlceras podem vir a cicatrizar apenas de duas a quatro semanas após o tratamento (Elad et. al., 2022).

A fase de ulceração é a mais significativa, devido à dor provocada ao paciente e por ser um ambiente propício para a colonização de organismos gram-positivos e negativos, expondo-o a bacteremias e sepse (Sonis, 2007). A reparação é a última fase do curso da MO e ocorre espontaneamente, a depender da condição sistêmica do paciente, resposta imunológica e presença de infecções oportunistas (Sonis, 2007; Shetty et al., 2022).

A perda de integridade da mucosa serve como porta de entrada para os microrganismos residentes na cavidade oral, levando, muitas vezes, a um quadro de bacteremia e sepse, especialmente em pacientes neutropênicos. Além disso, a inflamação gerada por produtos das células inflamatórias subjacente a área ulcerada provoca intensa dor e desconforto para o paciente (Singh, Singh, 2020).

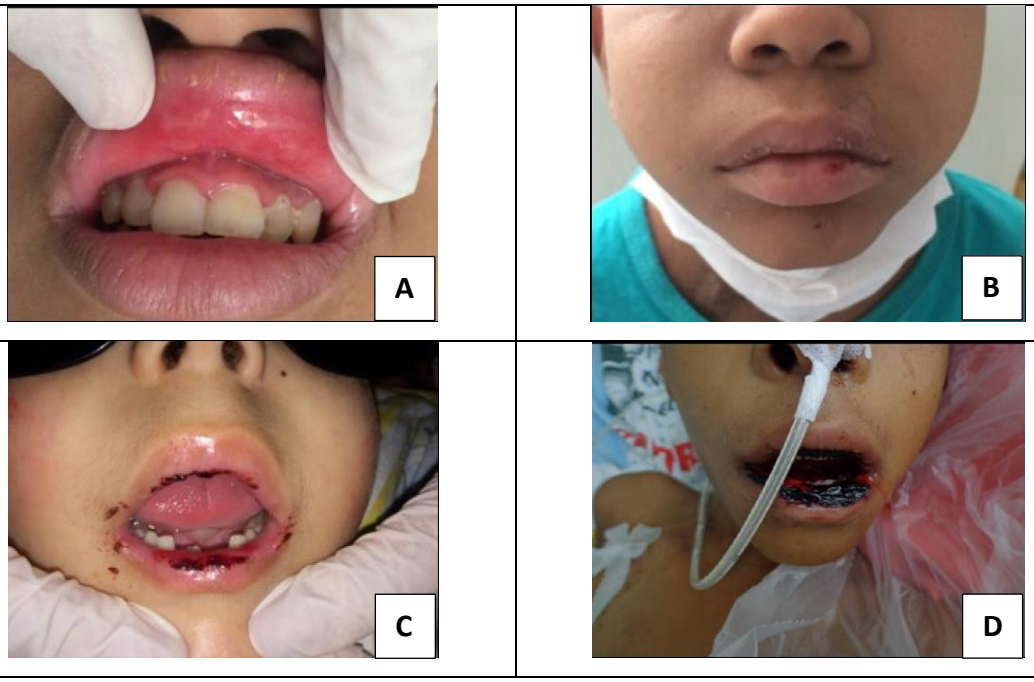
Na fase do reparo, que ocorre espontaneamente, os fibroblastos e a angiogênese desempenham um papel importante na regeneração do tecido. A matriz extracelular sinaliza a migração, proliferação e diferenciação do epitélio até sua completa reparação. É importante mencionar que, mesmo após a reparação da ferida, o local ainda está vulnerável a uma nova ulceração, uma vez que o

remodelamento dos tecidos ainda não se completou e vão receber nova injúria no ciclo seguinte de QT ou RT (Sonis, 2007).

O ciclo de renovação das células da mucosa oral tem duração de sete a 14 dias (Shetty et al., 2022). Os primeiros sinais da MO ocorrem cerca de três a cinco dias do início da QT e, em seguida, surgem as úlceras, atingindo a intensidade máxima das lesões entre sete e 14 dias e cicatrização após uma semana (Villas, Sonis; 2015).

Vale ressaltar que a mucosa oral, por ter uma rápida taxa de renovação celular, frequentemente apresenta complicações agudas como a MO, enquanto o tecido ósseo tende a apresentar complicações tardias, uma vez que possui uma taxa de renovação celular mais lenta (Devi, Singh, 2014; Ray-Chaudhuri, Shah, Porter, 2013).

Figura 1. Apresentação clínica da mucosite oral, de acordo com a escala da OMS. A. Irritação e eritema na mucosa labial superior (Grau 1). B. Úlcera no lábio inferior; dieta sólida (Grau 2). C. Úlceras nos lábios; dieta líquida (Grau 3). D. Úlcera no lábio inferior; dieta parenteral (Grau 4).



Fonte: própria dos autores.

2.4 Ocorrência da mucosite oral em crianças e adolescentes

A ocorrência da MO pode variar a depender se a doença de base do paciente é um tumor hematológico ou sólido (Ribeiro et al., 2020; Docimo, Anastasio, Bensi, 2022). Damascena et al. (2020) verificaram que o tempo médio para ocorrer a MO em pacientes com tumores sólidos foi duas vezes maior quando comparado com pacientes com tumores hematológicos. Além disso, os fatores de risco para ocorrência da MO foram distintos entre os pacientes com tumores sólidos e hematológicos. Ribeiro et al. (2020) também observaram diferenças a partir da 6ª semana de tratamento nas alterações orais de pacientes com tumores sólidos e hematológicos. Estes últimos apresentaram alterações mais severas.

Embora crianças e adolescentes apresentem maior chance de desenvolver MO, elas também apresentam uma cicatrização mais rápida dessas lesões, devido à elevada atividade mitótica das células da mucosa oral (Qutob et al., 2013; Otmani, Hattad, 2021). Portanto, é possível verificar diferença na incidência da MO em uma mesma faixa etária, sendo esta comorbidade mais frequentemente observada em indivíduos maiores de dez anos (Attina et al., 2021).

2.5 Identificação da mucosite oral em pacientes pediátricos

A maioria dos estudos com crianças e adolescentes em tratamento quimioterápico avaliam a MO por meio da escala da OMS (Docimo, Anastasio, Bensi, 2022). Ela combina critérios objetivos (presença de eritema e úlcera), subjetivo (queixa de dor) e funcional (tipo de dieta), atribuindo ao paciente códigos de 0 (ausência de alterações) a 4 (presença de úlcera, dor e impossibilidade de ingerir alimentos sólidos, pastosos ou líquidos) (Tomlinson et al., 2008).

A escala *National Cancer Institute's Common Terminology Criteria for Adverse Events* (NCI-CTCAE) avalia qualquer evento desfavorável, sinal, sintoma ou doença associado a um procedimento ou tratamento médico, incluindo a MO. Este instrumento combina critérios subjetivos e funcionais, cujos escores variam de 0 (ausência de alterações) a 5 (morte) (National Cancer Institute, 2022).

A *escala Children's International Mucositis Evaluation Scale (Chimes)* é um instrumento confiável e validado para avaliação da MO em crianças, o qual avalia subjetivamente sete elementos: dor; capacidade de engolir, falar e beber; uso de medicamentos para dor; e presença de úlceras na cavidade oral. A dor e os aspectos funcionais são medidos por meio de expressões faciais que vão de um

rosto feliz (1) a triste/chorando (5). Os demais itens são avaliados por meio de perguntas dicotômicas e direcionadas ao cuidador (Jacobs et al., 2013).

O *Oral Mucositis Daily Questionnaire* (OMDQ) é um instrumento que coleta o relato do próprio paciente quanto ao histórico de dor na boca ou orofaringe nas últimas 24 horas e quanto a dor nessas regiões afeta os hábitos de dormir, engolir, beber, comer e falar. Além disso, também questiona o histórico de diarreia nas últimas 24 horas. Essas informações também são medidas por meio de expressões faciais que vão de um rosto feliz (1) a triste/chorando (5) (Tomlinsom et al., 2011).

O *Oral Assessment Guide (OAG)* é um instrumento que avalia objetivamente a MO em crianças e adolescentes com câncer por meio da inspeção visual, palpação, audição e observação de oito itens referentes a cavidade oral, cujos escores variam de 1 (sem alteração) a 3 (alteração severa). Os itens avaliados são: voz, engolir, lábios, língua, saliva, mucosa jugal/palato, gengiva e dentes (Gibson et al.; 2006).

Outro instrumento validado para essa faixa etária é o *Oral Mucositis Assessment Scale (OMAS)*. Ele busca identificar de forma objetiva a presença de úlceras e eritema em nove regiões (lábio superior e inferior, bochecha direita e esquerda, ventre e lateral da língua em ambos os lados, assoalho, palato mole e duro). O eritema é categorizado em ausente (0), não severo (1) ou severo (2), enquanto a úlcera é avaliada de acordo com o tamanho (em cm^2) em códigos que vão do zero (ausência de úlcera) até 3 (> $3cm^2$). Além disso, essa escala também avalia a presença de infecção, dor oral, capacidade de engolir e o tipo de dieta (Sung et al., 2007).

Inicialmente, as escalas da OMS, NCI-CTCAE e OAG foram desenvolvidas para a população adulta, no entanto a OMS e NCI-CTCAE podem ser utilizadas para todas as faixas etárias e o OAG foi validado para crianças e adolescentes (Gibson et al., 2010; Docimo, Anastasio, Bensi, 2022).

Diante das diversas escalas e seus diferentes critérios, a incidência e severidade da MO podem apresentar variações, bem como o parâmetro do sucesso do tratamento para cada escala (Docimo, Anastasio, Bensi, 2022; Sonis, 2022).

2.6 Diagnóstico diferencial da mucosite oral

A estomatite aftosa recorrente, úlceras traumáticas, líquen plano (ulcerativo), doenças vesiculobolhosas com repercussão na cavidade oral e lesões malignas em

boca são exemplos de doenças que fazem diagnóstico diferencial com a MO (Shetty et al., 2022).

O diagnóstico da MO baseia-se na confirmação da instituição da terapia oncológica, bem como no aspecto clínico, tempo e localização das lesões (Scully, Sonis, Diz, 2006). Nos estágios iniciais, verificam-se áreas eritematosas que provocam sensação de ardência e, após o rompimento do epitélio, surgem úlceras profundas, irregulares, frequentemente cobertas por uma pseudomembrana de células mortas e microrganismos (Villa, Sonis, 2020).

Geralmente, a MO acomete áreas cujo epitélio oral é do tipo não queratinizado (Shetty et al., 2022). A MO induzida pela QT raramente afeta o dorso da língua, palato duro e gengiva. Enquanto no tratamento radioterápico, o palato duro pode ser afetado (Scully, Sonis, Diz, 2006). Vale ressaltar que, em casos raros, a MO pode durar por até três meses após o RT (Villa, Sonis, 2020).

As infecções virais também podem causar lesões semelhantes à MO, porém elas são tipicamente erodidas, localizadas, envolvem áreas de mucosa queratinizada e os pacientes, muitas vezes, apresentam febre. Caso não seja possível definir o diagnóstico, é recomendada a realização de citologia esfoliativa e/ou cultura (Scully, Sonis, Diz, 2006; Shetty et al., 2022).

A doença do enxerto contra o hospedeiro (DECH) e a MO podem ocorrer simultaneamente em pacientes que realizaram TCTH e, neste caso, o diagnóstico requer avaliação do histórico médico, verificação do estado nutricional e do uso de imunomoduladores (Shetty et al., 2022).

2.7 Repercussões e manejo da mucosite oral na saúde dos pacientes oncopediátricos

Em decorrência da agressão da mucosa resultante da QT e RT, o paciente com MO pode apresentar sensação de ardência da mucosa, necessitando de um controle dietético, evitando-se alimentos duros, picantes/condimentados, bebidas ácidas/cítricas e enxaguatórios com álcool (Scully, Sonis, Diz, 2006; Singh, Singh, 2020).

A partir do surgimento das úlceras, faz-se necessário o controle da dor por meio de substâncias anestésicas e analgésicos não opioides, opioides ou a combinação deles de acordo com a severidade da dor (Donohoe et al., 2018; Attina et al., 2021).

Os pacientes pediátricos também podem apresentar dificuldade ao falar, engolir, comer, beber e dormir devido a dor causada pela MO (Cheng et al., 2012; Kamsvåg-Magnusson 2014). Consequentemente, esses pacientes estão sujeitos a perda de peso severa, desnutrição e necessidade de suporte nutricional enteral e parenteral (Otmani, Hattad, 2021).

Além disso, o surgimento das úlceras prejudica a higienização da cavidade oral (Shetty et al., 2022). No sentido inverso, há evidências de redução da gravidade e na dor, devido à MO quando os pacientes recebem orientação e realizam regularmente a higiene oral (Miranda-Silva et al., 2021).

O tratamento oncológico é capaz de quebrar a homeostasia entre o hospedeiro e a microbiota oral, levando ao crescimento de microrganismos patogênicos e, consequentemente, exacerbando a resposta inflamatória e promovendo a ocorrência de MO (Ji et al., 2022). Por sua vez, o rompimento da barreira epitelial e exposição do tecido conjuntivo subjacente permite a entrada de microrganismos, aumentando o risco de agranulocitose, bacteremia ou sepse (Villa, Sonis, 2019; Triarico et al., 2022).

Com isso, os pacientes com MO necessitam de analgésicos, anestésicos, antimicrobianos, suporte nutricional, internação hospitalar, consultas médicas, exames complementares e outros recursos que resultam em custos para os hospitais (Villa, Sonis, 2020; Alsheyyab et al., 2021).

A MO é uma condição bastante debilitante e está associada ao aumento da mortalidade de pacientes submetidos ao TCTH (Elad et al., 2022). Os pacientes transplantados com MOG apresentam mais toxicidades relacionadas ao tratamento oncológico e maior incidência de infecções. Consequentemente, uma redução na gravidade e duração dessas lesões podem impactar substancialmente na morbidade e mortalidade (Gabriel et al., 2003).

Cerca de 85% das crianças com MO necessitam de hospitalização (Otmani, Hattad, 2021). De acordo com Allen et al. (2018), o tempo de hospitalização pode aumentar em 4,6 dias para cada aumento em uma unidade do escore da MO. Sendo que, por exemplo, um dia de internação de um paciente com MOG custa, em média, $2.176 dolares americanos (Alsheyyab et al., 2021).

Portanto, todas essas complicações da MO podem contribuir para a interrupção do tratamento oncológico e afetar seu prognóstico (Lalla et al. 2019). A vigilância

em saúde realizada por uma equipe de saúde bucal foi capaz de reduzir 81,9% das interrupções do tratamento quimioterápico devido à MOG (Ribeiro et al., 2021).

De acordo com *Mucositis Study Group of the Multinational Association of Supportive Care of Cancer and International Society of Oral Oncology* (MASCC), as principais medidas no manejo da MO em crianças e adolescentes com câncer são a implementação de cuidados orais básicos, crioterapia e fotobiomodulação (Hong et al., 2019; Miranda-Silva et al., 202; Patel et al., 2021).

Segundo Bezerra et al. (2021), a implementação de um programa de educação e prevenção em saúde bucal pode reduzir a incidência de MO e, devido à falta de estudos de alto nível de evidência, tem sido aconselhado por diretrizes de prática clínica (Miranda-Silva et al., 2021).

Uma revisão sistemática recente com metanálise demonstrou que a fotobiomodulação pode ser utilizada na prevenção e no tratamento da MO em crianças e adolescentes, reduzindo a dor e a severidade das lesões. No entanto, os estudos são muito heterogêneos quanto ao protocolo de aplicação (Redman, Harris, Phillips, 2022).

3 OBJETIVOS

Objetivo Geral:

- Identificar a ocorrência de mucosite oral, suas escalas de mensuração, o impacto deste agravo no tempo de hospitalização e fatores associados em pacientes oncológicos pediátricos.

Objetivos específicos:

- Descrever características clínicas e laboratoriais de crianças e adolescentes com leucemia afetadas pela mucosite oral grave durante o tratamento quimioterápico;
- Verificar o impacto da mucosite oral no tempo de internação em crianças e adolescentes com câncer;
- Discutir as escalas de mensuração da mucosite oral utilizadas em crianças e adolescentes com câncer;
- Caracterizar e identificar a incidência da mucosite oral em crianças e adolescentes com câncer;
- Analisar fatores de risco da mucosite oral em crianças e adolescentes em tratamento quimioterápico.

4 RESULTADOS

Nesta seção, serão apresentados quatro artigos científicos classificados nos quatro primeiros estratos do Qualis Capes, de acordo com a Classificação dos Produtos PPGO Quadrienal 2017-2020 e/ou Quadriênio 2013-2016, na seguinte ordem:

- Artigo 1: Oral Mucositis in Children with Hematologic Tumors Undergoing Chemotherapy: A Case Series;
- Artigo 2: The Length of Hospital Stay and the Severity of Oral Mucositis in Pediatric Cancer Patients: A Systematic Review;
- Artigo 3: How to Assess Oral Mucositis in Children Undergoing Antineoplastic Therapies?;
- Artigo 4: Incidence and Severity of Oral Mucositis in Oncopediatric Patients Undergoing Chemotherapy: A Short-term Prospective Cohort.

4.1 ARTIGO 1 - Oral Mucositis in Children with Hematologic Tumors Undergoing Chemotherapy: A Case Series

O manuscrito a seguir foi submetido para publicação no periódico "**Pesquisa Brasileira em Odontopediatria e Clínica Integrada**" (Classificação A4 no quadriênio 2017- 2020 / Classificação B3 no quadriênio 2013-2016 / Indexada no WEB OF SCIENCE EMERGING SOURCES CITATION INDEX (ESCI), SCOPUS, SCIELO, DOAJ (Directory of Open Access Journals), SCIMAGO JOURNAL RANKING, REDALYC, LILACS e BBO / Fator de Impacto 1,554) e encontra-se em análise.

TITLE

Oral Mucositis in Children with Hematologic Tumors Undergoing Chemotherapy: A Case Series

Fabio Gomes dos Santos, Paula Maria Maracajá Bezerra, Nayara Pereira Limão, Ynnaiana Navarro de Lima Santana, Isabella Lima Arrais Ribeiro, Paulo Rogério Ferreti Bonan, Eliane Batista de Medeiros Serpa, Simone Alves Sousa, Ana Maria Gondim Valença

ABSTRACT

Oral mucositis (OM) is the most common local adverse event of chemotherapy treatment and leads to a debilitating condition from the patient's perspective. The aim of this study was to report nine cases of OM over 10 weeks after initiating chemotherapy in pediatric patients with leukemia. More of the patients were male (n=5, 55.6%), had black/brown skin (n=5, 55.6%), with ALL (n=6, 66.7%), and the mean age was 5.55. Two patients had values below normal for leukocytes, platelets and creatinine over the 10 weeks of follow-up. However, all patients showed changes in normality of hematological data in most week. The most used chemotherapeutic agents were aracytin, etoposide and methotrexate, known for their high stomatotoxic potential. Patients had 2 to 6 (mean of 4) episodes of SOM and 4 to 7 (mean of 5,5) episodes of OM. One patient at week 7, one patient at week

5, and one patient at weeks 2 and 10 did not have OM. Saliva (84 times) and lips (44 times) were the most affected items. Therefore, It is possible to plan more effective actions from knowledge of the possible risk factors for OM in order to decrease the prevalence of the condition. Observational studies are suggested to better elucidate the risk factors for early onset SOM.

KEY WORDS: oral mucositis, hematologic diseases, case reports, children, chemotherapy.

INTRODUCTION

Leukemias are hematological tumors of unknown origin which transform normal blood cells in the bone marrow into non-functional and rapidly proliferating cells through a genetic mutation. Acute Lymphoid Leukemia (ALL) is the most common in young children and Acute Myeloid Leukemia (LMA) affects children and adults, but its incidence rises with increasing age. Acute injuries are treated through a combination of chemotherapy drugs and conducted in stages according to the type of tumor [1].

Oral mucositis (OM) is the most common local adverse event of chemotherapy treatment in children and adolescents, however it also affects the patient's systemic condition, leading to a debilitating condition from the patient's perspective. In this regard, appropriate management of OM must be taken into account during the course of therapy [2,3,4]. Oral mucosal damage caused by chemotherapy tends to be acute, reaching its peak within two weeks after starting treatment [4].

Younger individuals are more likely to develop oral mucositis than adults because of the rapid epithelial mitotic rate; however, the healing process occurs more rapidly than in adults for the same reason [5].

There are different risk factors potentially involved in the development of oral mucositis in pediatric patients, being considered a multifactorial event. The risk factors considered are: chemotherapeutic agents, underlying disease, specific individual characteristics, hematological, renal and hepatic parameters, genetic profile and biomarker factors, and oral microbiota [6].

Understanding how risk factors relate to the occurrence and duration of OM is crucial to prevent the interruption of medical treatment and increase the likelihood

of a patient's cure. Therefore, the aim of this study was to report nine cases of oral mucositis in children undergoing chemotherapy for leukemia for 10 consecutive weeks.

CASE SERIES

The procedures performed in this study were observed by the Ethics Committee for Research with Human Beings of the Health Sciences Center of the Federal University of Paraiba, under the protocol number: CAAE: 64249317.3.0000.5188, and conducted in accordance with the ethical principles of the Declaration of Helsinki. All the children gave their assent to participate and informed consent was obtained from all their parents or legal guardians.

Medical reports of nine patients of both genders, between 2 and 16 years old were included, diagnosed with Acute Lymphoid Leukemia (ALL) or Acute Myeloid Leukemia (AML) and who were followed for a period of 10 consecutive weeks between April 2013 and July 2015 in the Pediatric Oncology sector at Napoleão Laureano Hospital, a reference center for prevention, diagnosis and cancer treatment, located in the northeast region of Brazil.

The reported cases are part of a sample of 105 patients between 2 and 18 years old with a diagnosis of solid and hematological tumors, but did not develop the severe form in the initial days of treatment. The primary outcomes results have been previously published [7].

Prior to the study, the patients should not have started antineoplastic treatment; they were expected to exclusively undergo chemotherapy treatment for the next 10 weeks; not have mucosal inflammation before starting chemotherapy and have severe oral mucositis (SOM) in the first week of follow-up.

More of the patients were male (n=5, 55.6%), had black/brown skin (n=5, 55.6%), with ALL (n=6, 66.7%), and the mean age was 5.5 ±4.4. Diagnosis of tumor type, chemotherapy regimen, type of blood and presence of metastasis were collected from medical records. Table 1 describes the characteristics of each patient.

All patients were newly diagnosed with the tumor, and were in the induction phase of cancer treatment. Aracityn (ARAC), Aracityn associated with Etoposide (AE) and Methotrexate (MTX) were the most commonly administered drugs during

the 10 weeks. Patients 4 and 6, both with AML, only used ARAC, while patient 1 (with ALL) only used MTX during data collection.

The hematological status of patients was collected weekly from medical records (Table 2). Patients 4 and 6 had values below normal for leukocytes, platelets and creatinine over the 10 weeks of follow-up. However, all patients showed changes in the normality of hematological data in most weeks.

Monitoring of the oral cavity was performed weekly using the modified Oral Assessment Guide (OAG) by a calibrated researcher (Kappa>0.85). The OAG is a simple and fast instrument applicable to children which assesses the following items through scores of 1 to 3: voice, swallowing, lips, tongue, saliva, oral/mucosal palate, labial mucosa, and gums. Scores 1 and 2 indicate normal and slight changes of oral structures and functions without lesions, respectively, while score 3 represents severe alterations in one or more items [8].

Patients had 2 to 6 (mean of 4) episodes of SOM and 4 to 7 (mean of 5,5) episodes of OM during the 10-weeks of follow-up. Patient 2 at week 7, patient 6 at week 5, and patient 8 at weeks 2 and 10 did not have oral mucositis (OAG=8). Lips and saliva were the most affected items.

As the patients already had SOM from the first week, they were treated with low-level laser therapy performed according to the protocol: wavelength of 660nm, power of 40mW, and dose of 4J/cm^2, applied locally for 30 s on reddish, erosive and/or ulcerated regions (ECCO Fibras e Dispositivos/Brazil – Model BM0004A). In addition, all patients received oral care instructions or treated other problems in the oral cavity.

DISCUSSION

In the present study, nine patients with ALL or AML who developed severe oral mucositis in the first week of chemotherapy treatment were selected. These patients showed oscillations between the mild/moderate and severe form of the lesion over the 10 weeks of follow-up.

The incidence of oral mucositis ranged 20% to 80% in oncopediatric patients [6]. Oral mucositis is the result of the stomatotoxic action of chemotherapy drugs or radiotherapy on the DNA of the basal cells of the oral epithelium, as well as from

damage to the adjacent connective tissue, leading to a series of biological events that culminate in the appearance of ulcerations [9].

Burning, dryness, erythema, edema, changes in the papillae, hoarseness and difficulty in swallowing are observed in the early stages [10,11]. Therefore, daily oral health surveillance is necessary when the objective is to prevent or minimize the clinical signs of oral mucositis.

On the other hand, we suggest that there are variables related to cancer treatment and variables related to the patient which apparently allow similar individuals to present different oral complications and intensity. The selected individuals in this study were similar in age, tumor type and chemotherapy regimen.

With regard to treatment-related variables, the occurrence of oral mucositis varies between 20% and 100% depending on the type of malignancy, chemotherapeutic drug type and chemotherapy regimen [12, 13]. Patients with hematological tumors are also at higher risk of developing oral mucositis when compared to patients with solid tumors [7].

Although treatment protocols for ALL and AML are different, the goal of treatment in the early stage is to achieve complete disease remission through a combination of chemotherapy. Then treatment is continued according to the type of cancer [1].

The drugs used in the treatment of the nine cases included the classes of alkylating, antimetabolites agents, natural products and miscellaneous. According to Sonis et al. (2004)[4], ARAC, MTX and Etoposide present the risk of 20, 23 and 20%, respectively, of developing severe oral mucositis. These were the drugs most used in the treatment of reported cases. Patients who undergo the same chemotherapy regimen may experience oral complications in different degrees depending on the dose and frequency of drug administration [10].

The cytotoxic effect of chemotherapeutic agents also depends on their mechanism of action, which may be specific for a phase of the cell cycle that requires prolonged exposure or repeated doses, or unspecific for the phase of the cell cycle and, therefore, more dose-dependent [14].

Patient-related variables such as age, nutritional status, type of mucosa, oral microbiota, oral health and hygiene status, salivary secretory function, neutrophil counts, molecularly targets and genetics can increase or reduce the risk for the severity of oral mucositis [15,16]. The variability in the factors that lead the patient

to develop oral mucositis, even in homogeneous and controlled samples, is a challenge in determining their risk [4].

The authors in a recent systematic review with meta-analysis highlighted the association of MTX with other drugs, oral microbiota and gene variants as important risk factors in the development of oral mucositis [6].

Garrocho-Rangel et al. (2018) [17] described a case series of 11 children with ALL followed for 14 days after treated with MTX as chemotherapy agent. However, none of them presented SOM. The changes occurred in the lips, tongue, buccal mucosa and gingiva. In our study, children were followed for 10 consecutive weeks after starting chemotherapy (including methotrexate) and developed severe oral mucositis in the first week of cancer treatment.

Some hematological parameters such as neutrophil, platelet and creatinine counts are possible risk factors for oral mucositis [6]. Neutropenic children are 7.5 times more likely to develop oral mucositis [18]. However, it is not possible to establish any association of hematological parameters with the occurrence and severity of oral mucositis in this study. The occurrence of oral mucositis was observed even in the patients whose blood rates are within the reference values.

The onset of oral mucositis may be early (4 to 7 days) or later, and its complete remission within 7 to 14 days after discontinuing the therapy [11]. The cases reported show alterations in the oral cavity between 1 and 11 days after the last dose of the chemotherapy. However, the brief appearance of such changes was due to the frequency of doses. The patient 3 received 3 doses of AD in the first week of treatment.

Damascena et al. (2018) [2] found that the remission time of severe oral mucositis was 30.6 days in oncopediatric patients. They also found that age (over 10 years old) and the absence of metastasis increase the duration of MOG by 1.4 times and 1.7, respectively.

Several methods have been used to manage OM, including Low-Level Laser Therapy, which has been found to reduce the incidence of any grade of OM by 90% (95% CI 0.81-1.00; p=0.06) and can reduce SOM duration [3].

Although the patients appeared to develop some degree of oral mucositis during the 10 weeks of follow-up, even with weekly applications of laser therapy, the clinical improvement of the patients was notable when compared to the time when the research group did not use this technology. Peng et al. (2020)[3] highlighted that

the risk of developing SOM was not significantly lower (p=0.13) with laser applications at 2-day intervals compared with that in the control group.

The Oral Assessment Guide (OAG), as well as the main toxicity scales, combine objective, functional and symptomatic aspects, applying them to eight specific anatomical areas [4]. Therefore, it is necessary to check the affected sites at each new exam to verify the improvement or worsening of the patient's clinical condition when using the OAG or a similar scale. In this study, the reduction in the OAG values was due to clinical improvement in the same affected sites, while worsening was due to the involvement of new sites in the oral cavity. Guimarães et al. (2021)[19] highlighted the importance of monitoring the likely sites most affected by SOM so that the strategies are more effective.

Most oral complications related to chemotherapy occur within the second week after starting treatment. The establishment of ulcerations causes discomfort and pain when speaking, swallowing, drinking and eating. In addition, the exposure of connective tissue associated with reduced care with oral hygiene due to pain makes the individual susceptible to infections in the oral cavity. Thus, the patient's systemic condition can worsen and lead to interrupting cancer treatment. However, it is possible to plan more effective actions from the knowledge of the possible risk factors for oral mucositis to reduce the incidence of this condition.

Due to the risk of oncopediatric patients presenting SOM early in treatment, well-designed observational studies are needed to better understand the risk factors for developing oral mucositis and the need for a multidisciplinary team to monitor pediatric patients undergoing chemotherapy to prevent and avoid worsening of this expected condition.

Authorship statement

All authors should have made substantial contributions to all of the following: Fabio Gomes dos Santos, Paula Maria Maracajá Bezerra, Isabella Lima Arrais Ribeiro, Simone Alves Sousa and Ana Maria Gondim Valença conceptualized and designed the study, was involved in analysis and interpretation of the data, drafted and revised the paper, and gave approval of the final version. Nayara Pereira Limão, Ynnaiana Navarro de Lima Santana, Eliane Batista de Medeiros Serpa and Paulo Rogério

Ferreti Bonan were involved in revising it critically for important intellectual content and final approval of the version to be submitted.

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Declaration of competing interest

The authors declare no conflicts of interest.

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TABLES

Table 1. Characterization of patients with leukemia and severe oral mucositis.

Patient	Gender	Age (Years)	Skin color	Hematologial tumor	Chemotherapy regimen	Bloodtype	Metastasis
1	Male	2	Black	ALL	MTX	A^+	No
2	Male	16	Black	ALL	AD/ARAC/AE	A^+	No
3	Male	4	Black	ALL	AE/ARAC	A^+	No
4	Male	3	Brown	AML	ARAC	A^+	No
5	Female	6	Brown	ALL	VD/ARAC/CP	A^+	No
6	Female	3	White	AML	ARAC	B^+	No
7	Female	9	White	AML	ARAC/AD	O^+	No
8	Female	3	White	ALL	MTX/AMC/ ARAC/CP/PM	O^+	No
9	Male	4	White	ALL	AE/ARAC	O^-	No

ALL = Acute Lymphoid Leukemia, AML = Acute Myeloid Leukemia, MTX = Metotrexate, AD = Aracityn+Daunoblastin, ARAC = Aracytin+Cytarabine, AE = Aracityn+Etoposide, VD = Vincristine+Daunorubicin, CP = Cyclophosphamide, AMC = Aracytin+Metotrexate+ Cyclophosphamide, PM = Purinethol+Metotrexate.

Table 2. Leukocyte count, platelet count and creatinine levels of patients with Leukemia.

Patient	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6			Week 7			Week 8			Week 9			Week 10		
	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C
1	N	↑	N	N	N	N	N	N	N	↓	↓	↓	↓	↓	↓	N	N	↓	↓	N	↓	↑	↓	N	↑	N	N	N	N	N
2	↓	N	↑	↓	N	N	N	N	↓	↓	↓	↓	N	N	↓	N	N	↓	N	↓	N	↓	N	N	↓	N	N	↓	N	N
3	N	↑	↓	N	N	N	↓	↓	↓	N	↓	↓	N	N	↓	↓	N	↓	N	N	N	↓	N	↓	N	N	N	N	N	N
4	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
5	N	↑	↓	N	↑	↓	↓	↓	↓	↓	↓	↓	↓	N	↓	↓	N	↓	↓	↓	↓	↓	↓	↓	N	↓	↓	N	↓
6	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
7	↓	N	↑	↓	↓	N	↓	↓	N	↓	N	N	↓	N	N	↓	↓	↓	↓	↓	N	N	N	↓	N	↑	↓	N	↑	↓
8	↓	N	↓	N	↑	N	N	N	N	↓	↓	N	↓	↓	↓	↓	↓	N	↓	↓	N	↓	N	N	↓	N	N	↓	N	N
9	N	↑	↓	N	N	N	↓	↓	↓	N	↓	↓	N	N	↓	↓	N	↓	N	N	N	↓	N	↓	N	↑	N	N	N	N

L = Leukocyte count, P = Platelet count, C = Creatinine, ↓ = Below normal value, N = Normal value, ↑ = Above normal value.

Table 3. Occurrence of oral mucositis, severe oral mucositis and affected sites of patients with Leukemia.

Patient	Affected sites by SOM and OM									
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	Tongue, saliva, gums	Lips, saliva	Saliva	Lips, saliva, labial mucosa	Lips, saliva	Saliva	Saliva	Lips, saliva	Saliva	Lips, saliva, labial mucosa
2	Lips, saliva	Lips, saliva	Lips, saliva	Saliva, oral mucosa	Lips, saliva, labial mucosa	Lips, saliva	No mucositis	Lips, saliva	Lips, saliva	Lips, saliva
3	Lips, saliva	Lips, saliva, labial mucosa	Lips, saliva, labial mucosa	Saliva	Lips, saliva	Saliva, labial mucosa	Saliva	Lips, saliva	Lips	Saliva
4	Saliva	Saliva	Lips, saliva	Saliva	All sites	Saliva	Saliva	Saliva	Saliva	Saliva
5	Lips, saliva	Lips, saliva	Lips, saliva	Lips, saliva	Lips, saliva	Lips, saliva	Saliva	Saliva	Lips, saliva	Saliva
6	Saliva, gums	Saliva, labial mucosa	Lips, tongue, saliva, oral mucosa, labial mucosa, gums	Lips, saliva	No mucositis	Saliva	Saliva	Saliva	Saliva	Saliva
7	Lips, saliva	Lips, saliva	Lips, saliva,	Saliva	Lips, saliva	Lips, saliva	Lips, saliva, oral	Saliva	Saliva	Saliva, labial

			oral mucosa, gums				mucosa, labial mucosa, gums			mucosa, gums
8	Lips, tongue, saliva	No mucositis	Saliva	Lips, saliva, labial mucosa	Saliva	Swalling, lips, tongue, saliva, labial mucosa, gums	Tongue, saliva, oral mucosa	Saliva	Tongue, saliva	No mucositis
9	Swalling, saliva	Saliva	Lips, saliva, labial mucosa	Lips, saliva	Lips, saliva	Lips, labial mucosa	Saliva	Lips, saliva	Saliva	Saliva

SOM = Severe Oral Mucositis (in blue), OM = Oral mucositis (in green)

4.2 ARTIGO 2 - The Length of Hospital Stay and the Severity of Oral Mucositis in Pediatric Cancer Patients: A Systematic Review

O manuscrito a seguir foi submetido para publicação no periódico **Supportive Care In Cancer** (Classificação A2 no quadriênio 2013-2016 / Fator de Impacto 3.603) e encontra-se em análise.

TITLE

The Length of Hospital Stay and the Severity of Oral Mucositis in Pediatric Cancer Patients: A Systematic Review

Fabio Gomes dos Santos; Thiago Isidro Vieira; Simone Alves Sousa; Isabella Lima Arrais Ribeiro; Paula Maria Maracajá Bezerra; Bianca Marques Santiago; Ana Maria Gondim Valença.

ABSTRACT

Cancer therapy can cause complications that generally require hospitalization, such as severe pain, fever, infections, hematologic disorders, nutritional deficiencies, and oral mucositis (OM), one of the most frequent and debilitating side effects. In this study, we investigated whether the severity of OM influences the length of hospital stay among pediatric cancer patients. The protocol for this systematic review was registered in the PROSPERO database (CRD42020157480). Two independent reviewers performed the searches in the Cochrane Library, Embase, LILACS, Open Grey, PubMed/Medline, Scopus, and Web of Science, using a combination of descriptors and synonyms following the PECO strategy. The Newcastle-Ottawa scale was used for the quality assessment and bias control, and the certainty of the evidence was assessed by the GRADE. The search strategy retrieved a total of 2,027 articles, of which 66 were selected for full-text reading and 3 were eligible for the qualitative synthesis. These were cohort studies with children and adolescents undergoing chemotherapy, published between 2012 and 2018. Only one of the included studies did not have a comparative group. The studies showed a low risk

of bias in all domains analyzed (selection, comparability, and outcome). OM was assessed using the scales of the World Health Organization (WHO) and the National Cancer Institute. One study found that for each increment in the degree/severity of OM measured by the WHO scale, the length of hospital stay increased by 4.6 days (P = 0.0005). The other selected studies reported that patients with grade III–IV OM on the WHO scale had more days of hospitalization and that only patients with grade 3 on the NCI scale required additional hospitalization. To conclude, the severity of OM may be an important factor associated with longer hospitalization. Yet, well-designed future studies are needed to confirm the quality of the available evidence.

Keywords: Stomatitis, Child, Neoplasms, Length of Hospital Stay.

Introduction

The clinical manifestation of oral mucositis (OM) in patients undergoing chemotherapy is commonly observed approximately 4 days after drug infusion. Patients initially experience mucosal atrophy, sensitivity, and erythema, which progresses to tissue ulceration and spontaneous healing [1]. Nearly 80% and 90% of children undergoing chemotherapy or bone marrow transplantation with myeloablative regimens develop OM lesions, respectively [2].

To date, there are no evidence-based protocols for the treatment of OM in children, but several therapeutic and preventive strategies have been studied [3]. The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISO) recognizes the potential of honey and photobiomodulation therapy in the management of OM, in addition to recommending the implementation of a basic oral hygiene protocol [4]. Only palifermin, a recombinant human keratinocyte growth factor 1 (KGF-1), was approved by the United States Food and Drug Administration for the prevention of OM in patients with hematologic malignancies receiving myelotoxic therapies and requiring hematopoietic cell support [1,5]. While palifermin can significantly reduce the severity of OM, it might not be clinically effective for milder lesions. In addition, rash, erythema, and white film coating of the tongue or mouth are adverse effects observed in children treated with palifermin. Therefore, the continuous

administration of this drug in children with cancer or undergoing HSCT is not recommended [6].

OM-related complications include changes in diet, weight loss, need for nutritional supplementation and opioid analgesics, increased risk of developing viral and fungal infections, interruption of cancer therapy, and additional hospital charges [6, 7, 8]. Thus, the management of OM aims primarily to control the symptoms and prevent or reduce the severity of oral lesions secondary to cancer therapy [9].

The management of OM usually requires the hospitalization of patients to treat or control these adverse effects. Otmani and Hattad (2021) [10] found that 84.8% of children with OM lesions required hospitalization. Thus, this systematic review aimed to synthesize the available evidence to determine whether the severity of OM influences the length of hospital stay among children and adolescents undergoing cancer therapy.

Methods

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [11] and The Synthesis Without Meta-analysis (SWiM) [12].

Eligibility criteria

The following inclusion criteria were considered: children and adolescents aged 0 to 19 years, undergoing antineoplastic treatment, hospitalized, and examined for the occurrence of OM lesions. The exclusion criteria consisted of studies that did not address the association between OM and the length of hospital stay; did not report or did not use a valid scale to assess the severity of OM; included adults in addition to children and adolescents; contained duplicated data from another included study; reviews, letters, books, conference abstracts, case reports, case series, opinion articles, technique articles, posters, and guidelines; scientific articles in non-Western languages; unavailable full-text, even after the corresponding authors were contacted.

Information sources

Literature searches were carried out in the following electronic databases: Cochrane Library, Embase, Latin American and Caribbean Health Sciences (LILACS), Open Grey, PubMed/Medline, Scopus, and Web of Science. The last searches were performed on December 31, 2021. The studies screened were not grouped for data synthesis.

Search Strategy

The search strategy was based on the acronym PECO, as follows: P (population) - children and adolescents undergoing antineoplastic treatment; E (exposure) - severe oral mucositis (SOM); C (control) - mild/moderate oral mucositis; O (outcome) – length of hospital stay.

Bibliographical searches were performed using MeSH terms and entry terms such as "child", "adolescents", "drug therapy", "radiotherapy", "oral mucositis" and “hospital stay”. The complete search strategy is shown in Supplementary Table 1. The reference list of included articles was manually screened for additional eligible studies. No filters were applied.

Study Selection and Data Collection

Retrieved search records were saved in RIS or BibTex formats and imported into the free web app Rayyan [13] for the removal of duplicates and the analysis of eligibility. Titles and abstracts were read and analyzed for their eligibility by two independent reviewers (FGS and SAS). When the information contained in the title and abstract was not sufficient to determine their inclusion or exclusion in the review, the full text was obtained. Then, the same two reviewers performed a full-text analysis of the remaining studies to select those eligible for the qualitative synthesis. In this process, any disagreement was resolved by consensus with the assistance of a third reviewer (TIV).

Data extraction

The following information was extracted from the articles included in this review: authors, country and year of publication, study design, groups, sample size,

age, tumor type, treatment modality, OM assessment, and main outcome. The corresponding authors were contacted by e-mail and/or through ResearchGate twice with an interval of two weeks to clarify or provide additional data for the article to be included or not in the quantitative analysis.

Effect measures

The length of hospital stay in relation to the severity of OM was expressed in absolute values, percentages, and/or Odds Ratio.

Risk of bias assessment

The risk of bias of the included studies was assessed using the Newcastle-Ottawa Scale for nonrandomized studies, which considers case-control and cohort designs. This scale uses a star system in which reviewers assess the risk of bias in the studies through three domains, namely: selection, comparability and assessment of the outcome. These domains have 4, 1, and 3 analytical items, respectively, and each item can be assigned one star, except for the comparability domain, which can be assigned two stars. Two independent reviewers (FGS and SAS) evaluated the included studies and resolved any divergences by consensus. In case of disagreement, a third reviewer (TIV) was requested to assist with the final decision.

Study grouping for data synthesis

All included studies were analyzed in the same period. No groupings of outcomes or study designs were used in the analysis.

Standardized metrics and data transformation

The metrics used to determine the relationship between the occurrence of SOM and the length of hospital stay reported by the included studies was the direction of effect.

Data synthesis

The vote counting method based on the direction of effect was applied for data synthesis. The vote counting was used to compare the number of studies that found a positive or non-positive association between the severity of OM and the length of hospital stay.

Criteria for data summary and synthesis

No specific criteria for data summary and synthesis were applied in this review.

Heterogeneity of reported effects

Data heterogeneity was assessed based on study design, age groups, chemotherapy regimen, co-interventions, and contextual/setting factors.

Certainty of evidence

The included studies were classified into different levels of evidence following the approach proposed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) via GRADEpro GDT (GRADEpro Guideline Development Tool [Software]; McMaster University, 2015, developed by Evidence Prime, Inc., available from gradepro.org).

Data presentation

The studies were ordered alphabetically in the tables. Table 1 presents a summary of descriptive characteristics of the sample, such as study design, sample size, statistical analysis, and main outcomes. Table 2 describes the risk of bias assessment for the selection, comparability, and outcome domains.

Results

Study selection

Database searches retrieved a total of 2,027 records, of which 134 were indexed in PubMed/Medline, 566 in Scopus, 48 in Web of Science, 60 in Cochrane Library, 342 in LILACS, and 877 in Embase. No articles were found in the Open Grey database. After duplicate records were removed, 1,419 articles were screened for eligibility based on their titles and abstracts. Of these, 1,353 articles were excluded due to the following reasons: out of the scope, non-eligible publication type, non-Western language, included adult participants and/or did not inform the age of the sample, or unavailable full text.

Sixty-six articles were selected for full-text analysis, of which 63 were excluded for not addressing the relationship between the length of hospital stay and the severity of OM or for recruiting patients older than 19 years. In total, three articles were included for data extraction (Table 1) and the qualitative synthesis, as shown in the PRISMA flow diagram in Figure 1. No study was retrieved from manual searches through the reference lists of included articles.

Table 1. Summary of descriptive characteristics of the included articles.

Study Characteristics			***Sample Characteristics***					***Statistical Analysis***	***Main Outcomes***	
Author, Year (Country)	**Study Design**	**Groups**	**Sample Size**	**Age group**	**Type of Tumor**	**Treatment modality**	**OM Assessment**	**Methods**	**OM prevalence**	**Hospitalization due to OM lesions**
Allen et al., 2018 (Australia)	Prospective Cohort	One group (repetitive times)	73	Children (not specified)	Hematologic, Solid, and CNS tumor	CT	NCI scale	Fisher exact, GEE, Logistic regression with GEE	42.50%	4.6 days/OM grade
Kapoor; Sinha; Abendin, 2012 (India)	Retrospective Cohort	HDMTX Control group	41 (HDMTX group) 85 (Control group)	1-18 years	ALL	CT and RT	WHO scale	Chi-square test, Cochran test, Mc Nemar test, Kaplan–Meier survival	38.93% (HDMTX group)	17.8% of patients with OM required additional hospitalization
Vitale et al., 2014 (USA)	Retrospective Cohort	Palifermin group Control group	25 (Palifermin group) 33 (Control group)	Children (not specified)	Hematologic, Solid, and CNS tumor	CT	WHO scale	Student's t-test , Chi-square test, Fisher's exact test	91.90% (control group) 80.00% (palifermin group)	Patients with Grade 3-4 OM had a longer hospital stay

Legend: HDMTX = High Dose of Methotrexate, ALL = Acute Lymphoid Leukemia, CNS = Central Nervous System, CT = Chemotherapy, RT = Radiotherapy, WHO = World Health Organization, NCI = National Cancer Institute scale, GEE = Logistic Generalized Estimating Equations.

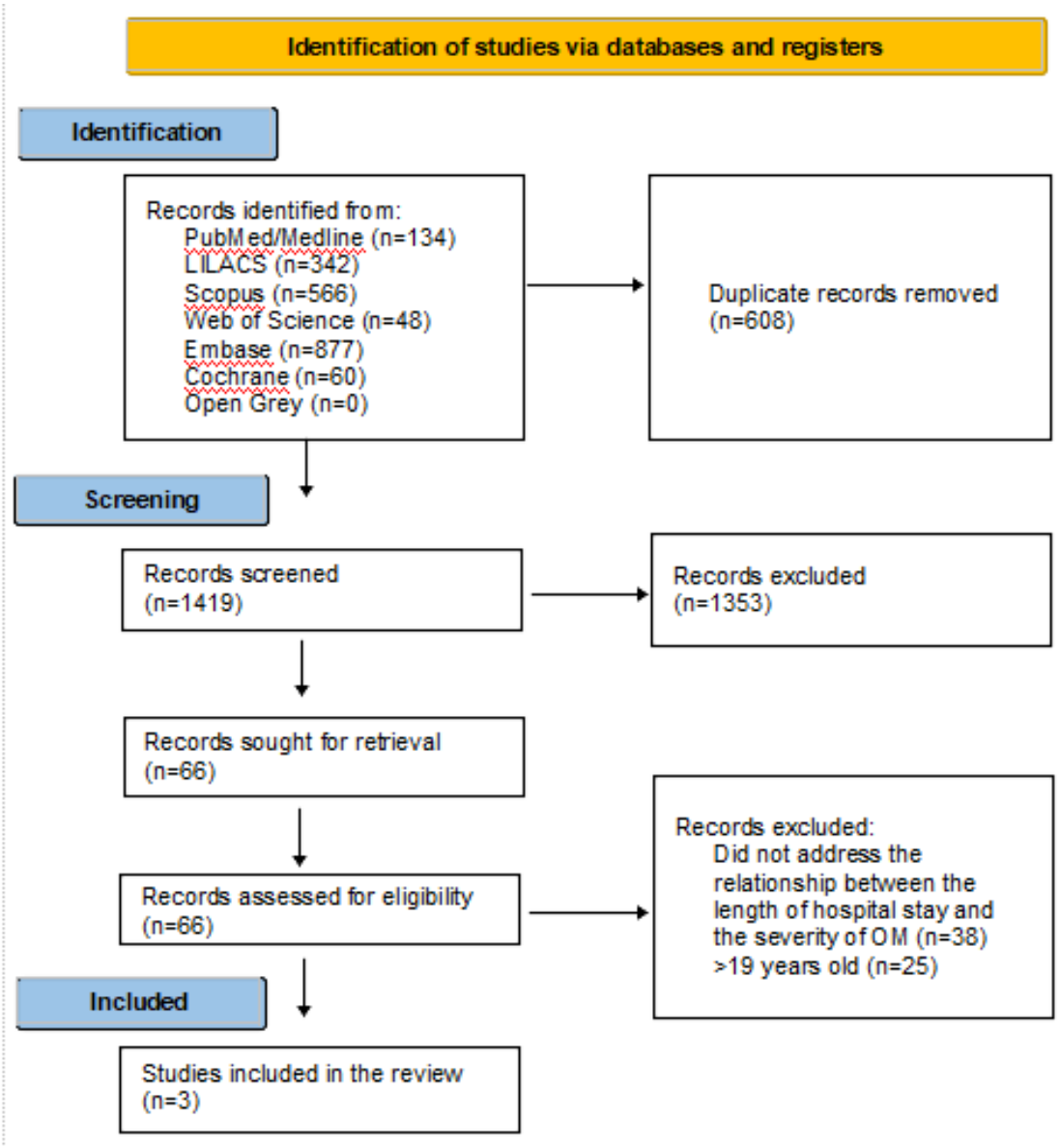

Figure 1. Flow diagram of the search strategy and study selection for new systematic reviews, according to the 2020 PRISMA guidelines.

Characteristics of included studies

The three included studies were carried out in Australia, India, and the USA, and were published between 2012 and 2018. The studies had a cohort design - one was prospective without a control group and the other two were retrospective with a control group. The follow-up time of patients is not clearly indicated in the studies by Kapoor et al. (2012) [14] and Vitale et al. (2014) [15]. Allen et al. (2018) [16] followed up the children for 14 days after chemotherapy excluding days 0, 1, and 2, on which there would be no risk of developing OM.

The sample size ranged from 25 to 85 children and adolescents (< 18 years old) per group. In the study by Kapoor et al. (2012) [14], the sample was divided into two groups, with and without high doses of methotrexate (HDMTX). In the study by Vitale et al. (2014) [15], participants were also divided into two groups, treated with palifermin and the untreated control.

The tumor type among participants was variable in each included study. Allen et al. (2018) [16] included patients diagnosed with a hematologic, central nervous system (CNS), or solid tumor malignancy, who received intravenous, intrathecal, and or subcutaneous chemotherapy (Berlin-Frankfurt-Munster or International Society of Paediatric Oncology protocol). Kapoor et al. (2012) [14] included only patients with a confirmed diagnosis of ALL who received HDMTX infusions (study group), and patients treated on a moderately aggressive protocol (modified MCP 841 protocol) without HDMTX (control group), both associated with prophylactic cranial radiation therapy. Vitale et al. (2014) [15] included patients with Hodgkin and non-Hodgkin lymphoma, solid tumors, and brain tumors who received chemotherapy under myeloablative conditioning regimens followed by Autologous hematopoietic stem cell transplantation (AHSCT).

The risk of developing OM in patients with hematologic malignancies was 7.0 and 7.1 fold higher compared to CNS and solid tumors (P = 0.008 and P = 0.0002), respectively. In addition, patients with Hodgkin lymphoma (HL) showed a significantly increased risk of developing SOM (OR, 5.41; 95% CI, 1.81-16.24, P = 0.003) when compared to patients with ALL, Acute Myeloid Leukemia (AML), CNS, and non-Hodgkin lymphoma (NHL) [16]. There was no statistically significant association between the risk of developing OM and HDMTX infusion (OR, 1.49; 95%

CI, 0.63-3.51; *P* = 0.362) [16] or plasma methotrexate levels at 42 h in patients under HDMTX therapy [14].

The diagnosis of OM was established based on the World Health Organization (WHO) scale in two studies [15,16] and the National Cancer Institute Toxicity Criteria CTCAE version 3.0 scale in one study [14]. Only one study [16] validated the calibration of the examiners, however, the authors did not report the statistical method for this purpose.

The prevalence of OM and SOM ranged from 35.15% to 86.20% and 13.79% to 32.75%, respectively [14, 15, 16]. In one study [14], the prevalence of OM was expressed as the number of episodes per cycle of treatment. According to Kapoor et al. (2012) [14], the onset of OM lesions occurred between 1 and 10 days (mean of 5 days), while for Allen et al. (2018) [16], receiving chemotherapy increased the risk of developing OM on the 8th (OR, 1.9; 95% CI, 1.1-3.3) and 9th days (OR, 1.8; 95% CI, 1.0-3.0). Moreover, these authors reported a statistically significant association with SOM (*P* = 0.0495) on the 3rd day.

Some measures to prevent the development of OM and/or mitigate the occurrence of other complications secondary to cancer therapy have been developed, including a standardized oral health protocol [16], leucovorin rescue for patients submitted to HDMTX [14], and the administration of palifermin [15].

Risk of bias (Quality Assessment)

The risk of bias in the included studies is presented in Table 2. In the “Selection” domain, two studies [14, 16] were not assigned a star due to the absence or non-description of the non-exposed cohort. Two studies [14, 15] did not indicate that outcome was not present at the start of the study. In the “Comparability” domain, all three studies were assigned only one out of two stars due to the lack of additional factors for the control group. As for the “Outcome” domain, all included studies were assigned a star for each of the three items.

Table 2. Quality assessment of included studies by the Newcastle-Ottawa Scale.									
	Selection				**Comparability**		**Outcome**		
	Item 1	*Item 2*	*Item 3*	*Item 4*	*Item 1A*	*Item 1B*	*Item 1*	*Item 2*	*Item 3*
Allen et al. (2018)	☆	×	☆	☆	☆	×	☆	☆	☆
Kapoor et al. (2012)	☆	×	☆	×	☆	×	☆	☆	☆
Vitale et al. (2014)	☆	☆	☆	×	☆	×	☆	☆	☆

Results of individual studies

All three articles included in this systematic review established a relationship between OM and the length of hospital stay. The occurrence of OM was associated with an additional hospital stay in 17.78% of the cases *(P* = 0.001) when compared to individuals without OM [14]. Patients with grade 3 or 4 OM were hospitalized for a longer period before and after stem cell transplantation, regardless of the use of a recombinant human keratinocyte growth factor, although the differences were not statistically significant [15]. Allen et al. (2018) [16] observed a significant association between the severity of OM and hospitalization. The authors reported that for each increment in the degree of OM, the patient's hospital stay increased by 4.6 days (95% CI, 2.0-7.1, *P* = 0.0005).

Results of data synthesis

All included studies [14 – 16] reported a longer hospitalization length in children/adolescents with more severe OM. Data heterogeneity was observed in the reported effects probably due to the use of different therapeutic regimens, undetailed age groups, and patient exposure to diverse co-interventions/settings.

Certainty of evidence

The GRADE assessment indicated a very low certainty of evidence in the included studies. As for the "risk of bias", all studies had at least one failure in the "selection" and "comparability" criteria. Hence, their risk of bias was considered to be “serious”. The “indirectness” criterion was also categorized as “serious” since the study population differed in terms of diagnosis and therapy regimen. In addition, the outcome was assessed in the studies using different scales. The “imprecision” criterion was considered “serious” due to the small number of events. “Inconsistency” was considered “non-serious” despite the clinical and methodological differences in the included studies, as their results indicated that patients with the most severe form of OM may experience longer hospitalization.

Table 3. Certainty of evidence of the included studies.

Certainty assessment							
№ of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Certainty**
3	Observational study	Serious[a]	Non-serious[b]	Serious[c]	Serious[d]	None	⊕◯◯◯ Very low

[a] = All included studies showed at least one failure in the Selection and Comparability criteria; [b] = The results of all included studies point to the same direction; [c] = Indirect intervention and outcome; [d] = Sample size smaller than 200 individuals.

Discussion

Only a few studies with children and adolescents undergoing cancer therapy have investigated the impact of the severity of OM on these patients’ hospitalization. Hence, most of the available evidence in the field was analyzed descriptively, making it unfeasible to carry out a meta-analysis.

The clinical course of OM begins with mucosal erythema and progresses to ulceration [17]. Several tools have been used to assess one or multiple aspects of OM lesions based on a rating scale [18]. In our review, all included articles used validated scales to assess OM lesions. The WHO scale and the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale are comparable regarding the severity of OM, with grades 1 and 2 considered as mild/moderate OM and grades 3 and 4 as SOM in both scales.

OM is one of the most debilitating side effects of cancer therapy (chemotherapy and radiotherapy). More severe lesions can dramatically affect eating, swallowing, speaking, and oral cleaning, and render the patient more prone to weight loss, dehydration, and infections [19].

Gibson et al. (2010) [20] recommended the Oral Assessment Guide (OAG), or its modifications, as the most appropriate scale to assess OM lesions in children and young individuals. The OAG and its modified versions are indicated for their intended assessment purpose, target population, specific outcomes, high quality, and ease of use. The OAG considers eight items related to the oral cavity (speech, swallow, lips, tongue, saliva, mucous membranes, gingiva, and teeth/dentures), each one with three possible scores: healthy, less healthy, and severe problem [21].

Patients with pain, infections, hematological alterations, and nutritional deficiencies generally need hospitalization. The length of hospitalization due to OM in children ranges between 8 and 22 days [22]. A study with 46 children and adolescents with chemotherapy-induced OM showed that 84.8% of participants required hospitalization and 71.7% of them had their cancer therapy delayed [10].

Importantly, patients can experience more than one complication resulting from cancer therapy. Kapoor et al. (2012) [14] reported that the main reasons for patient readmission were febrile illness and grade 3 OM lesions. Moreover, patients with mucositis were 2-fold more likely to develop a fever (95% CI, 1.3-3.2). These two conditions together led to a 7% increase in the length of hospital stay. In contrast, patients with OM lesions without fever did not require hospitalization.

Hospitalization of critically ill children promotes deterioration of oral health characterized by an increase in biofilm accumulation, gingival inflammation, and oral mucosal lesions [23]. Thus, cancer therapy cycles may have to be postponed until patients can recover from these complications [19]. A study carried out with 105

pediatric cancer patients followed up for 10 consecutive weeks found that 66.6% of the causes of chemotherapy interruption were related to SOM [24].

We note that although some studies [22, 25] have observed a delay in cancer therapy in pediatric patients, it is not possible to state, based on the available evidence, that it is a direct result of OM. Depending on the chemotherapy regimen, the intervals between cycles can be longer than a week. Therefore, the patient can present an episode of OM without compromising the planned treatment since oral alterations are often resolved [24]. Generally, mucosal lesions are completely healed within 7 to 14 days [26].

Kapoor et al. (2012) [14] found that the delay in the next cycle of cancer therapy was longer in patients with OM than otherwise *(P* = 0.315). Furthermore, patients in the first cycle who developed mucositis were more likely to develop it in the following cycles *(P* = 0.160).

The pathogenesis of OM involves both direct DNA damage or direct drug diffusion through the basal layer of the oral epithelium, or via the saliva, and indirectly through the release of inflammatory cytokines and metalloproteins in the extracellular milieu [27, 28]. Therefore, the Multinational Association of Supportive Care in Cancer (MASCC) recommended the implementation of oral hygiene practices as an important preventive measure for OM [29]. Consistent with this, Ribeiro et al. (2020) [30] observed a reduction of 81.8% in the number of SOM-related chemotherapy interruptions after the implementation of an integrated oral healthcare protocol for pediatric cancer patients.

Chemotherapy drugs are the main risk factors for the development of OM, whether at low or high doses [31, 32]. Nevertheless, in the study by Allen et al. (2018) [16], no association was observed between the administration of high doses of methotrexate and the occurrence of OM. Compliance with a series of measures that involve clinical monitoring, hydration, urine alkalinization, plasma methotrexate level monitoring, and leucovorin rescue is essential for HDMTX therapy [14]. Sajith et al. (2019) [25] reported that the likelihood of presenting toxicity was 12.72-fold greater with an increase in the dose of methotrexate.

In a recent systematic review [31], the development of OM in oncopediatric patients has been mainly associated with chemotherapeutic agents, as well as the underlying disease; specific individual factors; hematological, liver, and renal parameters; genetic profile and biomarker factors; and oral microbiota. Allen et al.

(2018) [16] found a statistically significant association between the occurrence of OM and the patient's diagnosis, type of treatment block of chemotherapy, days of chemotherapy administration, administration of pain medication to control oral pain, and neutropenia. Kapoor et al (2012) [14] noted that patients who developed OM had a significantly higher occurrence of fever and elevation of transaminases.

The occurrence of OM also has remarkable economic implications. For pediatric patients (≤ 18 years) admitted with severe mucositis, the mean cost of hospital resources was estimated at USD 2,176 per admission [33]. Because of the high economic burden associated with the management of OM, the adoption of preventive measures can be rewarding even if some of them are expensive, given the serious consequences of OM [34].

In their most recent guidelines, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) reviewed all published interventions for the management of OM in pediatric patients (anti-inflammatory; antimicrobials, mucosal coating agents, anesthetics, and analgesics; basic oral care; cryotherapy; growth factors and cytokines; photobiomodulation; and natural and miscellaneous agents). They concluded that there is still limited or conflicting evidence about the available protocols, but the implementation of a basic oral hygiene protocol has been considered beneficial [4].

This systematic review has important limitations to consider, such as the small number of primary studies and the low level of evidence in the included studies. Consistent with the fact that conducting well-designed randomized clinical trials with children and adolescents with cancer is challenging, no clinical study has determined the impact of OM on the length of hospital stay in this population. Prospective randomized clinical trials have the highest level of scientific evidence for being able to establish causality between intervention and exposure [35]. None of the included studies had this study design, in which two were retrospective cohorts and one prospective. The interpretation of findings requires parsimony, since both OM and length of hospital stay are multifactorial outcomes. The studies included in this systematic review did not address all possible factors associated with each of these outcomes.

Finally, it is worth mentioning that, currently, immunotherapy may be a promising therapy in cancer treatment [36], either by boosting the immune system or directly targeting the malignant cells [37]. Some studies have shown that patients

treated with immunotherapy have a lower prevalence of OM compared to traditional chemotherapy agents [36]. However, none of the included studies evaluated patients undergoing this new therapy.

Our findings may encourage researchers to examine this association for evidence-based practice of the multidisciplinary team and caregivers in terms of diagnostic surveillance, prevention, and early treatment of OM. Collectively, this can provide patients with a better quality of life and support decision-making regarding financial resources.

Conclusion

To conclude, the severity of OM may be an important factor associated with longer hospitalization. Yet, well-designed future studies with a robust statistical analysis are needed to confirm the quality of the available evidence.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Fabio Gomes dos Santos, Thiago Isidro Vieira and Simone Alves de Sousa. The first draft of the manuscript was written by Fabio Gomes dos Santos and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This is a systematic review, and no ethical approval is required.

Consent to participate

This research does not involve human subjects, and no written informed consent is required.

4.3 ARTIGO 3 - How to Assess Oral Mucositis in Children Undergoing Antineoplastic Therapies?

O manuscrito a seguir foi submetido para publicação no periódico **Evaluation & the Health Professions** (Fator de Impacto 2.329 e indexado na EMBASE, MEDLINE, Scopus e Web of Science) e encontra-se em análise.

TITLE

How to Assess Oral Mucositis in Children Undergoing Antineoplastic Therapies?

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ABSTRACT

Oral mucositis (OM) is the most common adverse effect of cancer treatment. Clinically, it manifests as atrophy, swelling, erythema and ulceration of oral tissue. The main instruments used to assess the severity of OM in patients undergoing chemotherapy and/or radiotherapy are based on identifying, by clinical exam, the changes in the oral mucosa epithelium that precede ulceration and the impact of these lesions on diet and pain reported by the patient. In the literature, there are few reliable and validated OM assessment tools for use in children and adolescents, most of which are derived from scales designed for the adult population. Based on the OM concept, all the main instruments can objectively grade it. Therefore, the Oral Assessment Guide (OAG) stands out from the others as it includes an objective assessment of the ability to swallow, talk and amount/consistency of saliva. Therefore, the instruments used to assess OM in children and adolescents undergoing antineoplastic therapies must identify the presence of oral mucosal ulcers and predict their risk factors in order to propose appropriate clinical interventions for the patient's well-being.

Key words: Oral mucositis; Child; Adolescent; Cancer.

Oral mucositis (OM) is the most common adverse effect of cancer treatment and, histologically, consists of direct or indirect damages in the epithelium of the oral mucosa (especially the non-keratinized) and submucosal. Clinically, it manifests as atrophy, swelling, erythema and ulceration of oral tissue (1, 2). The appearance of these lesions in the patient generates discomfort/pain, affecting the ability to speak, swallow and eat (3). In addition, patients with OM require medications to control pain and infections, prolonged hospital stays, nutritional support, and the treatment may be interrupted or modified (3, 4, 5, 6).

The prevalence of OM and Severe Oral Mucositis (SOM) in children and adolescents undergoing to chemotherapy (CT) can reach approximately 90% and 35%, respectively (4). The risk of OM in this age group is higher when compared to adults due to a higher rate of cell proliferation (3) and in hematologic malignancies when compared to solid tumors (4). Oral complications in oncopediatric patients are attributed cause of morbidity and potential mortality (7).

The most common scales available in the literature for classification OM in children are the World Health Organization (WHO) scale, and the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE). Only a few studies use the Oral Assessment Guide (OAG) or modifications. Although these instruments were not initially developed to be used in children, the OAG has been validated for these individuals (4, 8).

The main instruments used to assess the severity of OM in patients undergoing CT and/or RT are based on identifying, by clinical exam, the changes in the oral mucosa epithelium that precede ulceration and the impact of these lesions on diet and pain reported by the patient (1, 2, 3). However, the development of OM goes beyond the effect of chemotherapeutic agents or radiation on biological tissues. Genetic profile and biomarker factors, oral microbiota, level of oral hygiene, and others are considered risk factors for OM (4).

The presence of ulcers favors the entry of microorganisms into the bloodstream and impairs the performance of adequate oral hygiene, making the individual susceptible to bacteremia induced by opportunistic pathogens (2, 9). According to Bezerra et al. (2021) (10), the implementation of an oral health education and prevention program can reduce the incidence of OM and, due to the lack of high level of evidence studies, it has been advised by clinical practice

guidelines (11).

In the literature, there are few reliable and validated OM assessment tools for use in children and adolescents, most of which are derived from scales designed for the adult population (1, 4, 7). The OAG is highly recommended for clinical and research purposes as it is a non-invasive method, especially for children, suitable for its purpose, its quality and ease of use (8).

The OAG, developed in 1988, assess the condition of the patient's voice, swallow, lips, tongue, saliva, mucous membranes, gingiva and teeth/dentures, through hearing, observation and palpation of these items, with or without the aid of a blade. Any change in normality in the eight categories of this scale can directly affect speech, eat/drink or cause discomfort/pain in the oral cavity (12).

Based on the OM concept, all the main instruments can objectively grade it. The presence of OM in the oral cavity explains the symptoms reported by patients when swallowing, eating, drinking, and talking (13). During cancer treatment, children and adolescents may complain of two or all of these symptoms simultaneously, especially in cases of SOM (14). Gibson et al. (2006) (15) adapted the OAG removing all mention of pain (subjective item) to make the instrument more reliable, changed the order of appearance of the categories, and suggested the addition of a separate pain assessment instrument. However, there is a lack of assessment of symptoms and their impact on patients' quality of life through validated patient-reported outcomes specific to OM and, consequently, on its proper management in a broader context (13). Therefore, the OAG stands out from the others as it includes an objective assessment of the ability to swallow, talk and amount/consistency of saliva.

Saliva has a mechanical and immunological function through its continuous flow that eliminates food residues and immunoglobulins, glycoproteins and other components that interfere with the growth of oral bacteria and fungi, respectively (16). The association between the severity of OM and salivary alterations is not yet clear in the literature, but patients undergoing CT or bone marrow transplantation may have alterations in the amount and viscosity of saliva or a lower incidence of SOM when exposed to salivary stimulation therapies (17, 18). However, salivary gland hypofunction and xerostomia are well-documented adverse effects of RT in patients with head and neck cancer (19, 20). Despite, there is no evidence that salivary flow stimulation prevents OM in children with hematological or solid cancer

treated with CT (21).

Chemotherapeutics may increase tissue toxicity in the salivary glands due to prolonged contact with drug-containing saliva (20). Also, the CT protocol (type of drug, dosage and schedule of administration) reflects the severity of the mucosal injury (16). Low salivary IgA, IgG and IgM concentrations may result in the development and potentiation of oral mucosal ulcerations (22). Furthermore, increased levels of inflammatory mediators and oral environment have been associated with OM (18, 23).

Therefore, saliva monitoring is essential for the control of other oral problems resulting from salivary alterations, such as caries and periodontal disease. Furthermore, the literature points out that the implementation of oral health promotion strategies can reduce the incidence of OM (10). The events involving the occurrence of OM occur simultaneously and are interconnected (16).

Early identification and, consequently, prevention of OM is the best way to treat it. Dysphagia caused by OM can further aggravate oral injuries and lead to fatigue, severe weight loss, anorexia, undernutrition and psychological symptoms (2, 3). Liquid or solid food intake may be partially or completely affected in patients with OM (24). Children may have difficulty expressing oral pain until lesions are well established (15). That is why the importance of a sensitive instrument in verifying discreet alterations not only in the oral mucosa but in vital functions for the individual.

It is worth mentioning that there are other causes related to the difficulty in ingesting food, such as nausea, lack of appetite, irritability, food preferences of the child, reflux disease and other conditions. In addition, difficulty in swallowing may be related to the type and location of the cancer. However, as the main cancers in children and adolescents are hematological, central nervous tumors, tumors of the abdomen, osteosarcoma, and rhabdomyosarcoma, assessing the patient's ability to swallow can be very useful in preventing OM for this age group.

The WHO scale for OM indirectly assesses the patient's ability to swallow by verifying the type of diet (solid or liquid), but it is not possible to attribute the cause to OM since other reasons can lead the patient to have difficulty in ingesting food.

In light of the foregoing, the OAG is an excellent instrument to objectively assess oral alterations caused by cancer treatment, especially CT, and should not be used to determine the prevalence of OM, since alterations in the categories "saliva", “voice" and "swallow" may overestimate its diagnosis. However, it can be

very useful to verify the severity of OM since these same categories make it a sensitive method to verify changes in the oral cavity associated with the development of these lesions.

In addition, OAG can be very useful in the indirect identification of OM in the oropharynx region, since the adverse effects of antineoplastic therapy can affect the entire mucosa of the gastrointestinal tract. It is worth mentioning that the NCI-CTCAE scale also assesses mucositis in other mucosae (8,15).

The identification of alterations by site makes it possible to know the areas most affected by OM and, consequently, which ones require preventive treatment and minimizes the severity from the early diagnosis of these lesions. Using the OAG, it was identified that the jugal/palate mucosa and labial mucosa were the sites most affected by SOM over 5 weeks (25). Whether on the one hand, evaluating several sites in the oral cavity may seem to be a disadvantage of use in children, as it requires a longer time for examination (26).

Therefore, the instruments used to assess OM in children and adolescents undergoing antineoplastic therapies must identify the presence of oral mucosal ulcers and predict their risk factors in order to propose appropriate clinical interventions for the patient's well-being. The WHO, NCI (CTCAE) and OAG are validity scales, capable of graduating OM, use both objective and subjective criteria, easy to use, inexpensive, and do not require calculation score. However, among mentioned scales, only the OAG assesses changes in the oral cavity by site and other aspects associated with occurrence of OM.

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4.4 Artigo 4 - Incidence and Severity of Oral Mucositis in Oncopediatric Patients Undergoing Chemotherapy: A Short-term Prospective Cohort

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TITLE

Risk Factors for Incidence and Severity of Oral Mucositis in Oncopediatric Patients Undergoing Chemotherapy: A Short-term Prospective Cohort

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ABSTRACT

Aim: To verify the risk factors for incidence and severity of oral mucositis (OM) in children and adolescents during anticancer treatment. Methods: A short-term prospective cohort was carried out with 105 patients aged zero to 19 years, followed for ten consecutive weeks and submitted to chemotherapy (CT) with or without another treatment modality. Sociodemographic variables were collected using a specific form, with CT regimens obtained from medical records and the oral cavity evaluated by Oral Modified Assessment Guide (OAG). Bivariate comparison tests were used to summarize data and test within- and between-group differences. The longitudinal changes in the participants' condition were modeled by mixed-model regression, using generalized estimating equations. Results: The incidence of mild/moderate and severe OM ranged from 43.8% to 64.8% and 16.2% to 31.4%, respectively. The sex, age, type of tumor, treatment modality did not statistically influence the severity of MO. The longer the time since the chemotherapy session, the lower the risk of presenting OM and SOM. However, the chances of OM or SOM not occurring at longer intervals between chemotherapy sessions were very low. In most patients who developed OM, the mild/moderate condition persisted for ten

weeks and the severe form for three weeks. Conclusions: Children and adolescents with cancer showed oscillations in the severity of OM during antineoplastic treatment and only the time since the last chemotherapy was statistically significant for severity of OM and OAG score.

INTRODUCTION

Childhood cancers differ from adult cancers in terms of etiology (which is not related to lifestyle, and only a few types are paternally inherited); lower rate of genetic mutation, and metabolic response to chemotherapeutic drugs (1). Their treatment can be through surgery, chemotherapy, radiotherapy, immunotherapy, and stem cell transplantation, depending on the type of tumor and stage (2). However, chemotherapy alone is the standard treatment for major cancers that affect children and adolescents or in combination with surgery or radiotherapy (3).

Several chemotherapy protocols are used in the treatment of children and adolescents, which may include a single or multiple highly toxic drugs due to their lack of specificity (4). Non-specific chemotherapeutic agents can cause cumulative systemic toxicity, worsened by the duration of treatment (5). Generally, the dose capable of killing cancer cells and causing toxicity in healthy tissues is borderline (4).

Oral mucositis (OM) is the most frequent toxicity in children and adolescents undergoing chemotherapy (6). They may develop OM in approximately 43% (7) to 64% (4) of cases. Meanwhile, the incidence of the severe form of oral mucositis (SOM) can range from approximately 9% (4) to 36% (8). Risk factors for the occurrence and severity of OM may be related to the patient (age, sex, nutritional and oral health status) or to the treatment (treatment modality, chemotherapy agent, dose, among others) (9).

The management of the patient during cancer treatment, with emphasis on OM, should be focused on the prevention and rapid treatment of ulcerations of the oral mucosa, since they predispose the patient to secondary infections by viruses, fungi, and bacteria. In addition, OM affects basic functions (such as eating, talking, drinking, and swallowing), impacts hospitalization time and cost, nutritional status, and quality of life (10).

Although there are several studies that evaluate the possible risk factors for the occurrence of OM in children and adolescents with cancer, they differ from each other. They do not present strong scientific evidence of their role in the development of OM (6, 11). De Farias Gabriel et al. (2021) (11) conducted a systematic review and meta-analysis to identify the risk factors associated with the development of OM in pediatric oncology patients and, as a limitation, they did not take into account the

risks for the severe form of OM. Therefore, the primary objective of this study was to verify the incidence and severity of OM in pediatric patients undergoing chemotherapy for 10 consecutive weeks, as well as the factors associated with its occurrence. The study hypotheses are that the incidence of OM and SOM differ during the follow-up and that the factors associated with the occurrence of OM are different from SOM.

MATERIALS AND METHODS

Study design

This study consists of a short-term prospective cohort, where subjects (oncopediatric patients) were identified, followed up and risk factors for the occurrence of the outcome (OM and SOM) were evaluated. It followed the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guideline for Reporting cohort studies" (12).

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was received by the Ethics Committee on Human Research under Presentation Certificate for Ethics Assessment number 12922113.8.0000.5188. All patients or legal guardians signed informed consent to be included in this study.

Setting

Children and adolescents with cancer were recruited from the pediatric oncology sector in Napoleão Laureano Hospital, located in João Pessoa, Paraiba, Northeast Brazil. This hospital is a reference center for prevention, diagnosis, and cancer treatment. The participants were selected between April 2013 and July 2015 and followed up for 10 consecutive weeks.

Participants

A convenience sample of inpatients and outpatients, both genders, between 0 to 19 years old, assisted by the Pediatric Oncology Service of the hospital was included in this study. The eligibility criteria were diagnosed and treated for some type of malignancy; did not start cancer treatment; were programmed to receive chemotherapeutic treatment for the first 10 weeks; did not received radiotherapy in the head and neck region; did not have inflammation of the oral mucosa before starting chemotherapy; and the caregiver gave consent for the child/adolescent to participate in the study.

The number of patients admitted in the pediatric oncology sector during the research period and who met the eligibility criteria determined the sample size.

Variables of the study

The dependent variables were obtained coded in an ordinal scale as without OM (score 0); mild or moderate OM (score 1); or SOM (score 2), in addition to the OAG score.

The independent variables of interest for this investigation were: sex (“male” / “female”), age (“0 to 12 years old”/ “13 to 19 years old”), local of residence (“principal city” / “Interior of State” / “Other State”), ethnicity (“White” / “Black” / “Brown” / “Indigenous”), baseline disease, type of tumor (“hematological” / “solid”), treatment modality (“Chemotherapy” / “Chemotherapy + surgery” / “Chemotherapy + radiotherapy” / “Chemotherapy + radiotherapy + surgery”), number of chemotherapy sessions (in days), period since the last chemotherapy (in weeks), death (“yes”/ “no”), oral assessment guide per site (“voice”, “swallow”, “lips”, “tongue”, “saliva”, “palate”, “labial mucosal”, “gingiva”), leukocytes and platelets counts and creatinine blood level (“normal”, “altered”), granulokine administration (“yes” / “no”), platelet concentrate infusion (“yes” / “no”), laser therapy (“yes” / “no”), and treatment interruption (“yes” / “no”).

Data source/measurement

The sociodemographic and clinical variables were collected from the medical records at the beginning of the research. The laboratory data were collected from the medical records once a week. The outcomes (OM and SOM) were evaluated

weekly, during a 10-week period, using the modified Oral Assessment Guide (OAG) (13) by one researcher calibrated (kappa>0.85).

At each follow-up week, all patients and caregivers were clinically evaluated and instructed to perform strict oral hygiene care. If OM was diagnosed (OAG score greater than or equal to nine, indicating at least one change in the oral mucosa), low-level laser therapy was performed according to the protocol: wavelength of 660nm, power of 40mW, and dose of 4J/cm^2, applied locally for 30 s on reddish, erosive and/or ulcerated regions (ECCO Fibras e Dispositivos/Brazil – Model BM0004A).

Thus, all the patients received oral health surveillance and were treated for OM and other oral problems. For this reason, this factor was controlled and the variables “oral hygiene”, “dental treatments” and “treatment of oral mucositis” were not included in the statistical analysis with the other variables.

The OAG scale was based on the assessment of eight items (voice, swallowing, lips, tongue, saliva, palate, labial mucosa, and gingiva) through scores of 1 to 3, which scores 1 indicates normal status, score 2 represents slight changes of oral structures and functions without lesions, and score 3 represents severe alterations. Each item is given a score (from 1 to 3), producing individual scores ranging from 8 to 24. If the total OAG value equals 9 or greater, it means that the patient has OM. If any of the eight items scores 3, then the patient was diagnosed with SOM (13).

The leukocyte, platelet and creatinine counts were considered normal whose values were between 3,500 and 10,000mm^3, 150,000 and 450,000mm^3, 0.5 to 1.0mg/dl; respectively. Values above or below normal were classified as "altered".

Statistical methods

Descriptive statistics and bivariate comparison tests were used to summarize data and test within- and between-group differences. Incidence rates were calculated for longitudinal data, including weekly cumulative incidences for each occurrence of OM or SOM during the 10-week follow-up.

The Poisson regression with robust error variance was used to model the recurrent data (the number of times the participant was diagnosed as having OM or SOM). Since different individuals had different numbers of recurrent events, the

Poisson regression assumes that the outcome (i.e., the number of events of interest that happen in a given interval) follows a Poisson distribution with a fixed rate of event occurrence over time. The effects of independent clinical variables (age, gender, and clinical factors) were expressed as incidence rate ratios (IRR and 95% confidence intervals) and tested for statistical significance.

Then, as the repeated longitudinal assessments were clustered among the participants, there was a violation of the assumption of independence of data. Hence, the longitudinal changes in the participants' condition were modeled by mixed-model regression, using generalized estimating equations (GEE). First, the original database was changed to a format that rearranges the groups of related columns (10-week assessments) into groups of rows in the new data file. The analysis was specified as binomial distribution, and Logit as the link function, in order to run the GEE model for the binary outcomes (OM and SOM), while for the OAG score a Gamma as the distribution and Log as the link function were used. GEE regression parameters were expressed as the odds ratio, at 95% confidence intervals, and the significance of the model effects was tested using Wald chi-square statistics.

All statistical analyses were performed using Microsoft Excel and IBM-SPSS 24.0 software, and statistical significance was set at $p<0.05$ to reject the null hypotheses.

RESULTS

From April 2013 to July 2015, were admitted to the hospital 115 new patients who met the eligibility criteria for the study. During this period, seven patients died, two were transferred to another hospital and one started radiotherapy in the head and neck region. A total of 105 children were included in this cohort study, 57 (54.3%) male and 48 (45.7%) female. Age ranged from 0 to 18 years (mean ± DP = 7.3 ± 5.2). Most of the children were of black or brown race (n=72; 68.6%), and residents in the countryside or other States (n=68; 64.8%). The main clinical features of the study sample are depicted in Table 1.

Concerning dental status, median (and interquartile range) values for DMFT and dmft indexes were 1.0 (2.0) and 0.5 (2.0) for children with permanent and

primary teeth, respectively. The number of chemotherapy sessions during the 10-week follow-up ranged from 3 to 10 sessions (mean ± DP = 5.9 ± 1.7).

The occurrence of OM and SOM was assessed at all ten consecutive weeks, and data were expressed as incidence rates. Summary data on OM is detailed in Table 2, showing that the incidences of OM ranged from 50.5% to 64.8%, and SOM ranged from 16.2% to 31.4% throughout the weekly assessments. When the participants' statuses were considered according to their weekly changes, a significant difference was only found between the first and second weeks (p=0.014) – 31 (29.5%) worsened their status.

From a total of 1050 assessments during the 10-week period, 252 (24.0%) observations were free from OM, in 547 assessments (52.1%) participants had OM, and in 251 assessments (23.9%) participants were diagnosed as having SOM. Therefore, the mean (and 95% confidence intervals) of the number of weeks with OM or SOM were 7.6 (7.1 – 8.1) and 2.4 (2.0 – 2.8), respectively. The distribution of the number of cumulative weeks of participants with OM or SOM is shown in Figure 1.

The number of weeks with OM was significantly higher (p=0.002) for younger participants (age range 1 – 12 years old) compared to older participants (age 13 – 19 years old). No influence of age was observed on the cumulative incidence of SOM (p=0.606). Moreover, the association between the number of weeks with OM or SOM and other independent variables (age, sex, tumor type, metastasis, and treatment modality) were tested using Poisson regression. No significant effect was found, except for the participant's age group (IRR = 1.26; 95%CI = 1.11 – 1.43; p<0.001).

Regarding the Oral Assessment Guide (OAG) assessment, Figure 2 shows the changes in the mean score values of the OAG categories throughout the 10-week follow-up. Summary data are detailed in Table 3, showing a higher number of scores 2 and 3 were observed for the categories "saliva" (mean ± DP = 1.83 ± 0.60) and "lips" (mean ± DP = 1.43 ± 0.69). The mean score of the overall categories was 1.23 (± 0.52). When the scores of all eight categories were summed, the summative score for the 105 participants ranged from 8.0 to 13.1 (mean ± DP = 9.76 ± 0.96). A slight significant increase in the summative OAG score was observed between the first (9.62 ± 1.6) and the second week (10.1 ± 1.9) (p=0.040), and no further changes were observed in the following weeks compared to the first week (p>0.05).

Then, multiple regression models for longitudinal dependent data were constructed to assess the influence of independent variables on the changes in the incidence of OM and SOM, and OAG scores. The final regression models using Generalized Estimating Equation are detailed in Table 4.

Only the time since the last chemotherapy was associated with the occurrence of OM (p=0.038; 95% CI: 0.95; 0.99), SOM (p=0.009; 95% CI: 0.96; 0.99) and OAG score (p=0.000; 95% CI: 0.996; 0.999).

DISCUSSION

Despite being a short-term cohort, studies with children with cancer with a follow-up of ten weeks or more are rare in the literature. The present study analyzed the sociodemographic, clinical and laboratory (hematological) aspects and cancer treatment-related characteristics that may influence the incidence and severity of OM in children and adolescents followed during the induction phase of cancer remission.

The therapeutic regimen of most protocols instituted at this stage is quite aggressive and, therefore, there is a greater susceptibility to adverse effects such as, for example, OM (14). The time since the last chemotherapy was shown to be a risk factor for OM (regardless of severity). While age, sex, tumor type and treatment modality did not influence the incidence and severity of OM.

In Brazil, it is estimated 7,930 new cases of childhood cancers per year in the triennium 2023-2025 being more prevalent in males and in the southern region of the country (15). In line with the epidemiological profile of Brazil, in the present study there was a predominance of male individuals. There is still no explanation in the literature for the greater propensity of males in the occurrence of childhood cancer however the presence of congenital defects may mediate the hypothetical causal association between them, especially in children under one year of age (16).

The patient's gender was not a variable that statistically influenced the incidence and severity of OM. Most studies in the literature do not present the frequency of OM according to sex in their results but Allen et al. (2018) (7), Attina et al. (2020) (17), and Carreón-Burciaga et al. (2018) (18) also found no statistically significant association between sex and OM, although it is more common among boys (18, 19).

In general, antineoplastic treatment acts on the direct or indirect destruction of cells with high mitotic activity, so, in addition to cancer cells, it causes damage to oral mucosa cells, especially in younger individuals whose cell renewal is more accelerated (20,21,22). Attina et al. (2020) (17) found a higher prevalence of OM in individuals older than ten years, however the sample consisted only of patients with solid tumors. In the study by Pratiwi, Ismawati and Ruslin (2019) (19), the prevalence was higher in patients with ALL younger than seven years. In addition to the higher frequency, Carreón-Burciaga et al. (2018) (18) observed greater severity in patients aged 2 to 5 years compared to those aged 6 to 12. In contrast, Allen et al. (2018) (7) did not find statistical significance between OM and age. In our study, although older children and adolescents were 3.38 more likely to have mild/moderate OM (p=0.001), it was not possible to accept the alternative hypothesis (CI 95%:1.68; 6.76). This result may reside in the fact that the sample was mostly composed of younger individuals (0 to 12 years old).

As for the type of tumor, in the regional and local scenario, solid tumors correspond to 56.9% of cases in the Northeast region of Brazil and 57.3% in the state of Paraíba (23,24). In the present study, the prevalence of hematological tumors was higher, since only Acute Lymphoblastic Leukemia (ALL) represented 40% of the sample.

Damascena et al. (2020) (25) found that the frequency of OM was higher in children and adolescents with hematological tumors and in those patients the appearance of lesions was twice as fast compared to solid tumors. Allen et al. (2018) (7) concluded that the chance of developing OM in cases of hematological tumors was seven times greater than in solid and central nervous system tumors. In the multivariable GEE analysis, the type of tumor (hematological or solid) did not statistically influence the incidence and severity of OM and OAG score.

It is important to note that there is no cut-off point in the OAG total score to determine the severity of OM. For this study, it was adopted that if the patient presented code 3 in at least one category of the instrument, the diagnosis of SOM would be established. A patient who scored 16, for example, could add code 2 to all eight items (diagnosis: mild/moderate OM) or code 1 to one item, code 2 to six items, and code 3 to another item (diagnosis: MOG). Therefore, the total value of the OAG can be useful in identifying one or more items in the oral cavity that need dental care.

The incidence, survival and mortality rate of childhood cancer has been poorly documented, especially in low- and middle-income countries due to the scarcity of vital statistical data and quality records (26). About 80% of children and adolescents with cancer are cured in high-income countries, while in other countries this rate is less than 30% (15).

The survival rate of the sample was higher than expected for high-income countries, however, the follow-up of patients was only two years. It is noteworthy that for cases of leukemia, kidney and liver tumors, the survival rate reduces to 73% among adolescents (3). ALL, Wilms Tumor and Osteosarcoma represented 60% of the sample in the present study.

Only a few types of childhood cancers are caused by environmental or lifestyle factors, most with no known cause. Therefore, prevention should focus on early diagnosis of injuries. However, in low- and middle-income countries, the survival rate was lower and are associated with delayed or imprecise diagnosis, unavailability of adequate treatment, treatment abandonment, death due to adverse effects and preventable disease recurrence (15).

Hospital Napoleão Laureano is in the capital of Paraíba (Northeastern Brazil) and is a reference in the state for cancer treatment. The implementation of the Health Care Network in oncology has favored early diagnosis and treatment of cancer through professional training and improved resources (23). However, in Brazil, large hospitals that perform more complex procedures perform better in health services and they are located in the South and Southeast regions, evidencing regional inequalities (27). In addition, the distance and cost of moving patients to specialized health centers are associated with delays in cancer diagnosis (28). About 64% of the sample resided in the countryside or in another state. Such variable may be indicative of a population whose access to health services is not adequate and contributes to a lower survival rate. However, the impact of place of residence and survival rate were not part of the scope of the present study and were included only for sample characterization.

Most of the study participants declared themselves as black or mixed race. The distribution of childhood cancer according to the skin color of the sample corroborates the hospital records of cancer in Brazil from 2000 to 2018, where the prevalence is higher in brown individuals in the Northeast, North and Center-West

regions (22). It is likely that genetic factors contribute to the risk of developing cancer in certain races/ethnicities.

OM, Candida and herpes simplex infections, dry lips, xerostomia/ hyposalivation, neuropathic pain, gingivitis, and caries are the main oral complications of cancer treatment in the infant population (29, 30).

The incidence of caries in both dentitions in children and adolescents during chemotherapy is higher than in healthy patients, being associated with changes in the quantity and quality of saliva and poor oral hygiene due to pain caused by OM, as well as emotional/psychological disorders (31). The oral condition of the patients, assessed at baseline using the DMFT and dmft indexes, showed a low experience of dental caries and was important to verify the oral health status before starting cancer treatment and designing a dental treatment plan. However, the study did not set out to verify its incidence, as the follow-up period was short to evaluate clinically detectable cavitations.

OM is a common and significant adverse effect of QT, RT and hematopoietic stem cell transplantation (HSCT), with prevalence varying according to regimen and type of treatment (32, 33). In children and adolescents undergoing chemotherapy the prevalence of OM can reach 90% in the mild/moderate form and 35% in the more severe form (34), being more frequent in this age group compared to adults due to the highest rate of cellular proliferation of the oral mucosal epithelium (22).

The incidence of OM was high during all follow-up weeks, being higher in the second week after the start of cancer treatment. SOM was observed in the first week and reached its highest incidence in the second and eighth weeks. There was a statistically significant difference in the incidence of OM only in the second week. The first signs of OM occur about three to five days after the start of chemotherapy, and then ulcers appear, reaching the maximum intensity of the lesions between seven and 14 days and resolution after a week (35).

Over ten consecutive weeks, patients underwent three to ten sessions of anticancer treatment. The initiation phase of OM begins immediately after the administration of QT or RT and a cascade of events is activated with each dose, being amplified and potentiated by molecular and cellular signals that result in tissue damage, prolonging the damage for days after the beginning of the antineoplastic treatment (36). Therefore, the incidence observed in patients can be explained by the cumulative effect of chemotherapy in the oral cavity.

The longer the time since the chemotherapy session, the lower the risk of presenting OM, SOM and higher values of OAG. However, the chances of OM or SOM not occurring at longer intervals between chemotherapy sessions are very low.

The risk of OM occurrence in children and adolescents has been related to the type of treatment (QT and/or RT), the therapeutic regimen (drug, dose, frequency of administration), patient-related factors (sociodemographic characteristics, genetic and epigenetic factors), systemic health parameters, oral health status, and tumor-related factors (11, 37).

Saliva was the OAG category that presented the most alterations (codes 2 and 3). Chemotherapy and radiotherapy can trigger acute or late effects on the salivary glands, leading to changes in saliva composition, reduced salivary flow, or xerostomia/ hyposalivation in cancer patients (38).

Saliva plays an important role in maintaining oral health by lubricating the mucosa, controlling dental demineralization, assisting in the composition of the resident microbiota, having antimicrobial action, and assisting in chewing, swallowing, and speaking, among other functions (39).

It is not clear in the literature whether salivary changes influence the severity of OM (40,41) or whether saliva stimulation works to prevent OM (42). However, from the clinical perspective of cancer patients, who are often physically and emotionally weakened, especially children, the multidisciplinary team must be aware of the repercussions of salivary changes on the patient's well-being during treatment.

Children and adolescents undergoing chemotherapy or stem cell transplantation have reported difficulty eating, swallowing, drinking, talking, and sleeping due to OM (43,44). Therefore, the OAG is an excellent instrument for evaluating the oral cavity of patients with cancer since, besides identifying erythema and ulcers, are evaluated saliva and patient's ability to speak and swallow.

The lip was the second category that most presented OAG codes 2 or 3. It is known that the lining mucosa of the oral cavity is more prone to develop OM lesions when compared to the keratinized oral mucosa (45). However, few studies report the occurrence of OM according to the affected region (46).

According to Costa et al. (2020) (40), the cheek/palate mucosa was the most affected site by SOM. Guimarães et al. (2021) (8) found that the cheek/palate mucosa, lips and labial mucosa were the sites most affected by SOM. Although

there are no explanations for the higher occurrence of OM in these sites, the knowledge of most affected sites by lesions are of paramount importance in preventing or controlling severity.

Given the heterogeneity in studies with children and adolescents with cancer, current scientific evidence does not allow conclusions about the effectiveness of interventions for OM in this population. Therefore, intervention protocols can be based on extrapolation of evidence of the adult population (33).

The use of substances that act as a physical barrier to protect the oral mucosa from irritation caused by cancer therapy were recommended in the prevention and treatment of OM (47). In addition, honey and vitamin E have also been used in the lip or oral mucosa hydration, but it was not possible to establish a guideline (33).

Currently, basic oral care has been suggested in the management of OM in cancer patients (48). Cryotherapy and photobiomodulation have been highly recommended for the prevention of oral and oropharyngeal mucositis in pediatric cancer and hematopoietic stem cell transplant patients (49).

It is worth mentioning that the hospital where the research was carried out does not have a dental team to monitor the oral health condition of hospitalized patients, and oral hygiene instructions and photobiomodulation were performed only once a week, according to the availability of the researcher who conducted the study.

Among the study limitations are the sample size and the absence of a control/comparison group. However, it should be noted that few studies have a sample of more than 100 patients, especially those followed for ten consecutive weeks and that cancer in children and adolescents is a rare condition. In addition, OM is an adverse effect that may occur concomitantly with other local and systemic changes in cancer patients, making it difficult to control confounding variables. However, such factors are controversial in the literature and, therefore, further studies are needed with children and adolescents with cancer with a low risk of bias and high scientific evidence. It is hard to conduct a study design that includes the various factors associated with the occurrence of OM described in the literature. Another limitation of the study was non-inclusion of the dose of chemotherapeutic agents.

Although, through a more robust statistical analysis, it was possible to identify the risk factors according to the severity of OM, taking into account the cumulative

406 effect of the antineoplastic treatment on the oral cavity over ten weeks of follow-up.
407 Still, no study in the literature evaluated the impact on the interval between
408 chemotherapy cycles and the occurrence of OM.
409
410 **CONCLUSION**
411
412 In summary, children and adolescents with cancer undergoing antineoplastic
413 treatment had a high incidence of oral mucositis during ten weeks of follow-up.
414 However, only the time since the last chemotherapy session are associated with the
415 appearance of these lesions and OAG score.
416
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Table 1. Main demographic and clinical characteristics of the study sample (n=105).

	Categories	n (%)
Sex	**Male**	**57 (54.3)**
	Female	48 (45.7)
Age groups	**0 – 12 years-old**	**81 (77.1)**
	13 – 19 years-old	24 (22.9)
Race	White	32 (30.5)
	Black	**22 (21.0)**
	Brown	**50 (47.6)**
	Indigenous	1 (1.0)
Local of residence	Capital city	37 (35.2)
	Countryside	**66 (62.9)**
	Other State	02 (1.9)
Baseline disease	**Acute Lymphoblastic Leukemia**	**42 (40.0)**
	Wilms Tumor	18 (17.1)

	Osteosarcoma	13 (12.4)
	Others	32 (30.5)
Type of tumor	Solid	51 (48.6)
	Hematologic	**54 (51.4)**
Treatment	**Chemotherapy**	**69 (65.7)**
	Chemotherapy + surgery	26 (24.8)
	Chemotherapy + radiotherapy	5 (4.8)
	Chemotherapy + radiotherapy + surgery	5 (4.8)
Number of chemotherapy sessions	3 – 4	22 (21.0)
	5 – 6	**48 (45.7)**
	7 – 8	29 (27.6)
	9 – 10	6 (5.7)
Death	**No**	**91 (86.7)**
	Yes	14 (13.3)

Table 2. Incidence rates of OM and SOM, severity scores, and changes in status according to the follow-up week.

	OM (%)	SOM (%)	OM + SOM (%)	Severity score – mean (95%CI)	Unchanged status	p-value*
1st week	60 (57.1)	19 (18.1)	79 (75.2)	0.93 (0.81 – 1.06)	–	–
2nd week	54 (51.4)	33 (31.4)	87 (82.9)	1.14 (1.01 – 1.28)	57 (54.3)	**0.014**
3rd week	46 (43.8)	29 (27.6)	75 (71.4)	0.99 (0.84 – 1.14)	43 (41.0)	0.158
4th week	56 (53.3)	28 (26.7)	84 (80.0)	1.07 (0.93 – 1.20)	52 (49.5)	0.314
5th week	62 (59.0)	21 (20.0)	83 (79.0)	0.99 (0.87 – 1.11)	45 (42.9)	0.391
6th week	46 (43.8)	31 (29.5)	77 (73.3)	1.03 (0.88 – 1.17)	52 (49.5)	0.702
7th week	56 (53.3)	22 (21.0)	78 (74.3)	0.95 (0.82 – 1.08)	75 (71.4)	0.214
8th week	46 (43.8)	33 (31.4)	79 (75.2)	1.07 (0.92 – 1.21)	62 (59.0)	0.107
9th week	68 (64.8)	17 (16.2)	85 (81.0)	0.97 (0.86 – 1.09)	72 (68.6)	0.096
10th week	53 (50.5)	18 (17.1)	71 (67.6)	0.85 (0.71 – 0.98)	63 (60.0)	0.056

* Changes compared to the previous week.

OM=oral mucositis; SOM= severe oral mucositis.

Bivariate comparison tests.

Table 3. Frequency of the scores of the Modified Oral Assessment Guide (OAG), according to assessed categories, throughout the 10-week period (% in parenthesis).

	Normal (score 1)	Slight changes (score 2)	Severe changes (score 3)	Mean (SD) score
Saliva	292 (27.8)	**647 (61.6)**	**111 (10.6)**	1.83 (0.60)
Lips	716 (68.2)	**216 (20.6)**	**118 (11.2)**	1.43 (0.69)
Labial mucosa	**927 (88.3)**	48 (4.6)	75 (7.1)	1.19 (0.54)
Tongue	**983 (93.6)**	38 (3.6)	29 (2.8)	1.09 (0.37)
Palate	**986 (93.9)**	43 (4.1)	21 (2.0)	1.08 (0.34)
Gingiva	**990 (94.3)**	35 (3.3)	25 (2.4)	1.08 (0.35)
Swallow	**999 (95.1)**	31 (3.0)	20 (1.9)	1.07 (0.32)
Voice	**1022 (97.3)**	16 (1.5)	12 (1.1)	1.04 (0.25)
Overall score	6915 (82.3)	1074 (12.8)	411 (4.9)	1.23 (0.52)
Summative score	–	–	–	9.76 (0.96)

Table 4. The estimated regression parameters of variables on the changes in the incidence of Oral Mucositis (OM), Severe Oral Mucositis (SOM), and Oral Assessment Guide (OAG) scores.

Dependent variable	OM		SOM		OAG score	
	Exp B (95% CI)	p-value	Exp B (95% CI)	p-value	Exp B (95% CI)	p-value
Intercept	2.30 (1.51; 3.51)	0.000	0.31 (0.20; 0.48)	0.000	9.29 (9.02; 9.57)	0.000
Sex (male)	1.63 (**1.00**; 2.64)	**0.048**	1.23 (0.82; 1.85)	0.314	1.03 (0.99; 1.06)	0.152
Age (older)	3.38 (**1.68**; 6.76)	**0.001**	1.25 (0.77; 2.04)	0.363	1.07 (**1.03; 1.12**)	**0.001**
Time after chemotherapy (weeks)	0.97 (0.95; 0.99)	**0.038**	0.98 (0.96; 0.99)	**0.009**	0.998 (0.996; 0.999)	**0.000**
Hematologic tumor	1.26 (0,77; 2.04)	0.349	1.16 (0.76; 1.77)	0.474	1.04 (**1.00; 1.07**)	**0.024**
Treatment (combined CTP + RT and/or surgery)	1.20 (0.47; 3.02)	0.696	0.71 (0.39; 1.30)	0.276	1.01 (0.95; 1.08)	0.675

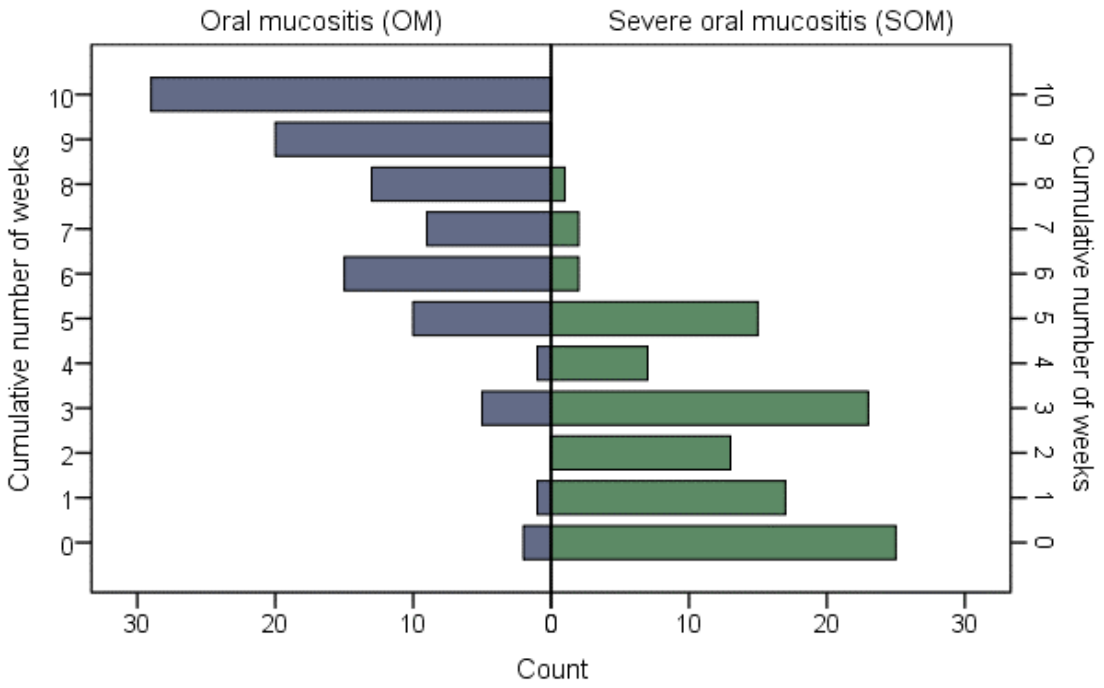

Figure 1. Cumulative number of weeks the participants (n=105) had OM or SOM during the 10-week weekly assessment (n=1050).

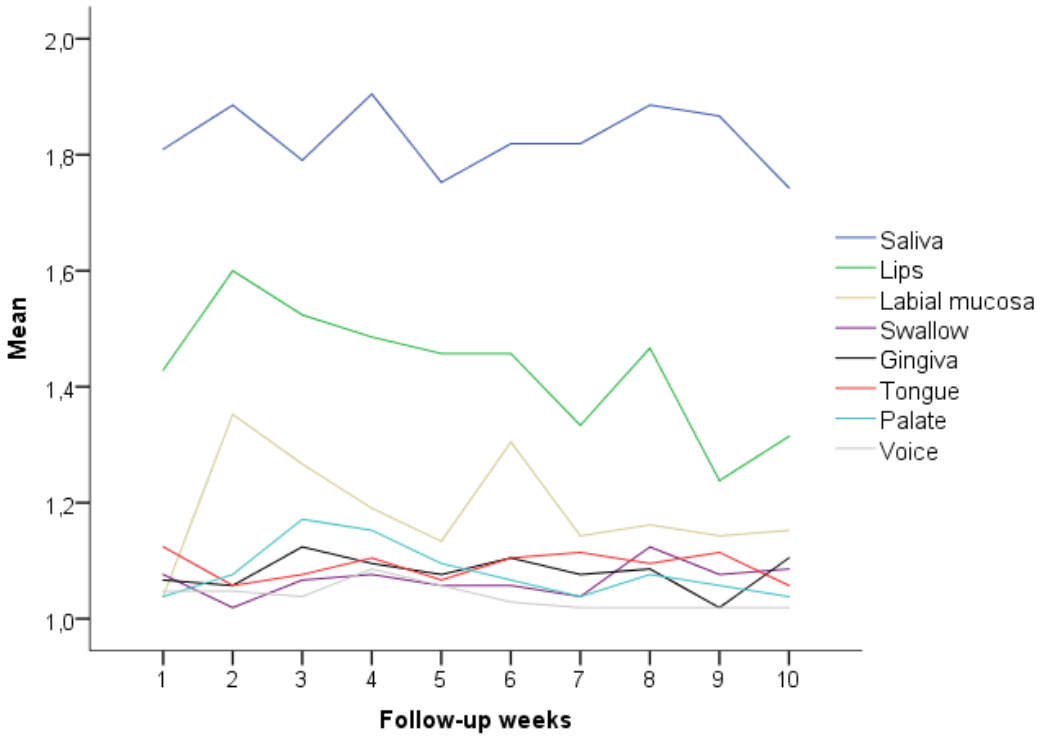

Figure 2. Changes in the mean score values of the OAG categories throughout the 10-week follow-up.

5 CONSIDERAÇÕES GERAIS

A pergunta norteadora para a elaboração dos artigos desta tese foi: a MO e a MOG apresentam os mesmos fatores de risco?

Sabe-se que a mucosite possui uma fase subclínica, em que ocorrem eventos moleculares e celulares imediatamente após a terapia oncológica, e uma fase clínica detectável após alguns dias (Sonis, 2009; Lalla et al., 2019). No entanto, uma porcentagem dos pacientes pode não desenvolver a MO durante o tratamento, outra desenvolve a forma mais leve/moderada e uma porcentagem menor apresenta a forma mais severa (Sonis, 2022).

A partir disso, revisitamos os dados coletados pelo nosso grupo de pesquisa e verificamos que, já na primeira semana, nove pacientes com tumores hematológicos do tipo leucemia desenvolveram MOG. Estes pacientes fizeram parte de um estudo previamente publicado (aprovação pelo CEP se encontra no Anexo 1 desta tese) com uma amostra de 105 pacientes entre dois e 18 anos diagnosticados com tumores sólidos e hematológicos (Ribeiro et al., 2020).

Optou-se por selecionar apenas os casos de leucemia, pois ela continua sendo a neoplasia mais comum e de maior causa de morte em crianças (Wu et al., 2022). Estudos recentes observaram maior prevalência de MO em crianças com tumores hematológicos, especialmente as leucemias (Allen et al., 2018; Miranda-Silva et al., 2022). Buscou-se, também, minimizar o viés do efeito citotóxico dos diferentes quimioterápicos, uma vez que os pacientes foram submetidos ao mesmo protocolo terapêutico.

Apesar das limitações desse tipo de estudo, os pacientes foram acompanhados por um longo período e foi possível explorar o impacto da MO em crianças e adolescentes com leucemia em tratamento quimioterápico.

A MO apresenta uma série de complicações que comprometem a qualidade de vida do paciente, sendo a maioria consequência da dor ou de infecções causadas pelas úlceras (Cheng et al., 2010; Cheng et al., 2012; Kamsvag-Magnusson et al., 2014). Os pacientes que desenvolvem essas alterações geralmente necessitam de hospitalização ou podem ter o tratamento oncológico interrompido, atrasado ou modificado (Donohoe et al., 2018; Alsheyyab et al., 2021; Otmani, Hattad, 2021).

Em um estudo publicado pelo nosso grupo de pesquisa, verificou-se que a interrupção na quimioterapia devido à MO superou as demais causas (Ribeiro et

al., 2019). No início da pandemia da Covid-19, a atuação diária e presencial da equipe de odontologia no hospital foi reduzida por medidas de biossegurança e, para minimizar essa ausência, foi instituído o telemonitoramento dos pacientes que apresentavam queixa de dor dentária ou por MO (Muniz et al. 2020; Damascena et al., 2022). Com isso, notou-se um aumento no número de casos de MOG em decorrência da redução na busca ativa de alterações iniciais da mucosa oral das crianças e adolescentes com câncer, a qual era proporcionada pelos pesquisadores por meio de ações de vigilância em saúde bucal.

Allen et al. (2018) verificaram que o aumento de cada escore da MO de acordo com a escala NCI-CTCAE aumenta em 4,6 dias o tempo de hospitalização. Contudo, isso pode estar associado também a outros fatores, como a febre neutropênica, alterações hematológicas, diarreia, perda de apetite, vômitos, dentre outras (Kamsvag-Magnusson et al., 2014; Allen et al., 2018; Otmani, Hattad, 2021).

Na literatura, há escassez de estudos que avaliem o impacto da MO no tempo de hospitalização do paciente. Logo, justificou-se a realização de uma revisão sistemática, cuja chave de busca encontra-se no Apêndice e o registro no PROSPERO no Anexo 2 desta tese para elucidar essa questão.

Os resultados desta revisão suscitaram outro questionamento. Existem na literatura mais de 54 instrumentos para avaliar a cavidade oral de adultos e crianças com câncer, sendo quatro para uso em crianças (Gibson et al., 2010). Entretanto, o principal instrumento para avaliar a MO em crianças e adolescentes continua sendo a escala da OMS (Docimo; Anastasio; Bensi, 2022). A ausência de um instrumento padrão pode alterar a prevalência e severidade da MO, uma vez que cada uma possui seus critérios diagnósticos, dificultando ou enviesando a síntese dos estudos (Docimo; Anastasio; Bensi, 2022; Sonis, 2022).

Há muitos anos o nosso grupo de pesquisa tem utilizado o OAG em suas pesquisas clínicas, pois percebemos ser ele um instrumento mais sensível as alterações na mucosa oral - além das lesões ulcerativas - e, devido seus critérios objetivos, pode ser aplicado às crianças mais jovens. Além disso, ele possui as seguintes vantagens: validade e confiabilidade para crianças e adolescentes, facilidade de uso, pode ser aplicado por toda a equipe multiprofissional, e pode ser usado na prática clínica e em pesquisas (Gibson et al., 2010). Outros pesquisadores também utilizaram o OAG em seus estudos (Tomaževič; Jazbec, 2013; Devi; Allenidekania, 2019; Otmani; Hattad, 2021).

Logo, decidimos analisar, de forma crítica, as principais escalas (Anexo 3) utilizadas para avaliar a MO em crianças e adolescentes com câncer, dando ênfase ao OAG, e divulgar esta análise sob a forma de uma *short communication* a fim de estimular novas pesquisas.

Por fim, buscou-se conhecer fatores de risco para MO e MOG por meio de uma coorte prospectiva de curto período e uma análise estatística robusta para desfechos contínuos. Após a análise completa dos dados, foi possível identificar os fatores de risco e de proteção para a ocorrência da MO e MOG. A escrita do manuscrito seguiu o *guideline* STROBE (Anexo 4). No entanto, a literatura ainda carece de estudos com evidência científica acerca do manejo da MO em crianças e adolescentes.

6 CONCLUSÕES

- As crianças e adolescentes com leucemia em tratamento quimioterápico podem desenvolver a mucosite oral grave já na primeira semana e apresentarem alternâncias na severidade da mucosite ao longo das 10 semanas de acompanhamento. Além disso, a saliva e os lábios foram os sítios mais acometidos. A partir desses achados, ressalta-se a necessidade da vigilância em saúde bucal logo no início do tratamento e da implementação de medidas preventivas para o manejo da mucosite oral nos casos de leucemias;
- A severidade da mucosite oral está associada ao aumento no tempo de hospitalização, no entanto, não há forte evidência científica. Logo, são necessários estudos primários com desenhos mais robustos que proporcionem maior evidência para pacientes oncológicos pediátricos. Há escassas revisões sistemáticas, com ou sem metanálise, para diferentes desfechos clínicos em crianças e adolescentes, sendo esta a primeira que buscou elucidar se a gravidade da mucosite oral influencia no tempo de hospitalização de crianças e adolescentes em tratamento oncológico. A resposta dessa revisão sistemática será útil na adoção de medidas preventivas e curativas visando uma melhor qualidade de vida aos pacientes e reduções nos custos hospitalares;
- O *Oral Assessment Guide* é um excelente instrumento para avaliar a cavidade oral de crianças e adolescentes com câncer em tratamento quimioterápico;
- As principais escalas utilizadas para avaliar a cavidade oral de crianças e adolescentes com câncer em tratamento quimioterápico são capazes de identificar a presença e severidade da mucosite oral. No entanto, não há uma escala padrão, dificultando a comparação entre os estudos, podendo este fato contribuir para a variabilidade na prevalência da mucosite oral entre eles;
- A incidência da MO e MOG em crianças e adolescentes com tumores sólidos e hematológicos, por meio do *Oral Assessment Guide,* foi alta ao longo de 10 semanas. Estes importantes achados devem ser considerados no manejo do paciente antes e durante o período de quimioterapia;
- A saliva e os lábios foram os sítios mais acometidos pelos escores 2 e 3 do *Oral Assessment Guide* em crianças e adolescentes com tumores sólidos e hematológicos em tratamento quimioterápico. Com isso, as escalas para a

mucosite oral não devem se restringir à avaliação de presença ou ausência de úlceras;

- Na maioria dos casos, a mucosite oral grave apresentou um curso clínico menor em comparação com a forma leve/moderada;
- O menor intervalo de tempo entre os ciclos quimioterápicos se constituiu em fator de risco para a ocorrência de MO, MOG e para o aumento do escore do OAG em crianças e adolescentes;
- Crianças e adolescentes do sexo masculino apresentaram menor risco para MO e para o aumento do escore do OAG;
- O aumento do escore do OAG foi menor entre as crianças e adolescentes do sexo masculino.

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* De acordo com as normas do PPGO/UFPB, baseadas na norma do *International Committee of Medical Journal Editors* - Grupo de Vancouver. Abreviatura dos periódicos em conformidade com o *Medline*.

APÊNDICE - Estratégia de busca do Artigo 2

Supplementary Table 1. Search strategy in electronic databases.	
Electronic database	**Search strategy**
Cochrane Library	Infant[MeSH Terms] OR Infant OR Infants OR Child, Preschool[MeSH Terms] OR Child, Preschool OR “Preschool Child” OR “Preschool Children” OR Child[MeSH Terms] OR Child OR Children OR Adolescent[MeSH Terms] OR Adolescent OR Adolescents OR Adolescence OR Teens OR Teen OR Teenagers OR Teenager OR Youth OR Youths OR “Female Adolescent” OR “Female Adolescents” OR “Male Adolescent” OR “Male Adolescents" OR Antineoplastic Protocols[MeSH Terms] OR “Antineoplastic Protocol” OR “Protocols, Antineoplastic” OR “Antineoplastic Protocols” OR “Cancer Treatment Protocols” OR “Cancer Treatment Protocol” OR Medical Oncology[MeSH Terms] OR “Medical Oncology” OR “Clinical Oncology” OR Drug Therapy[MeSH Terms] OR “Drug Therapy” OR “Therapy, Drug” OR “Drug Therapies” OR “Therapies, Drug” OR Chemotherapy OR Chemotherapies OR Pharmacotherapy OR Pharmacotherapies OR Radiotherapy[MeSH Terms] OR Radiotherapy OR Radiotherapies OR “Radiation Therapy” OR “Radiation Therapies” OR “Radiation Treatment” OR “Radiation Treatments” OR “Targeted Radiotherapies” OR “Targeted Radiotherapy” OR “Targeted Radiation Therapy” OR “Targeted Radiation Therapies”[Title/Abstract]
Embase	((infant OR infants OR "Child, Preschool" OR "Preschool Child" OR "Preschool Children" OR child OR children OR adolescent OR adolescents OR adolescence OR teens OR teen OR teenagers OR teenager OR youth OR youths OR "Female Adolescent" OR "Female Adolescents" OR "Male Adolescent" OR "Male Adolescents" OR "Antineoplastic Protocol" OR "Protocols, Antineoplastic" OR "Antineoplastic Protocols" OR "Cancer Treatment Protocols" OR "Cancer Treatment Protocol" OR "Medical Oncology" OR "Clinical Oncology" OR "Drug Therapy" OR "Therapy, Drug" OR "Drug Therapies" OR "Therapies, Drug" OR chemotherapy OR chemotherapies OR pharmacotherapy OR pharmacotherapies OR radiotherapy OR radiotherapies OR "Radiation Therapy" OR "Radiation Therapies" OR "Radiation Treatment" OR "Radiation Treatments" OR "Targeted Radiotherapies" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy" OR "Targeted Radiation Therapies")) AND ((stomatitis OR stomatitides OR "Oral Mucositis" OR oromucositis)) AND (("length of stay" OR "Stay Length" OR "Stay Lengths" OR "Hospital Stay" OR "Hospital Stays" OR "hospitalization time" OR "hospitalization period"))
Latin American and Caribbean Health Sciences (LILACS	tw:((tw:(infant OR lactente OR lactante “preschool child” OR “pré-escolar” OR preescolar OR child OR criança OR niño OR adolescent OR adolescente OR “antineoplastic protocol” OR “protocolos antineoplásicos” OR “cancer treatment protocol” OR “clinical oncology” OR oncologia OR “oncología médica” OR “drug therapy” OR “tratamento farmacológico” OR quimioterapia OR chemotherapy OR pharmacotherapy OR radiotherapy OR radioterapia)) AND (tw:(“oral mucositis” OR estomatite OR stomatitis OR estomatitis)) AND (tw:(length of stay OR “tempo de internação” OR “tiempo de internación”)))
Open Grey	(Infant OR “Preschool Child” OR Child OR Children OR Adolescent OR “Antineoplastic Protocol” OR “Cancer Treatment Protocols” OR “Cancer Treatment Protocol” OR “Medical Oncology” OR “Clinical Oncology” OR “Drug Therapy” OR Chemotherapy OR Pharmacotherapy OR Radiotherapy) AND (Stomatitis OR “Oral Mucositis”) AND (length of stay OR “Hospital Stay” OR “Hospital Stays” OR "hospitalization time" OR "hospitalization period")

PubMed/Medline	((Infant[MeSH Terms]) OR Infant[Title/Abstract]) OR Infants[Title/Abstract]) OR Child, Preschool[MeSH Terms]) OR Child, Preschool[Title/Abstract]) OR “Preschool Child”[Title/Abstract]) OR “Preschool Children”[Title/Abstract]) OR Child[MeSH Terms]) OR Child[Title/Abstract]) OR Children[Title/Abstract]) OR Adolescent[MeSH Terms]) OR Adolescent[Title/Abstract]) OR Adolescents[Title/Abstract]) OR Adolescence[Title/Abstract]) OR Teens[Title/Abstract]) OR Teen[Title/Abstract]) OR Teenagers[Title/Abstract]) OR Teenager[Title/Abstract]) OR Youth[Title/Abstract]) OR Youths[Title/Abstract]) OR “Female Adolescent”[Title/Abstract]) OR “Female Adolescents”[Title/Abstract]) OR “Male Adolescent”[Title/Abstract]) OR “Male Adolescents"[Title/Abstract]) OR Antineoplastic Protocols[MeSH Terms]) OR Antineoplastic Protocols[Title/Abstract]) OR “Antineoplastic Protocol”[Title/Abstract]) OR “Protocols, Antineoplastic”[Title/Abstract]) OR “Antineoplastic Protocols”[Title/Abstract]) OR “Cancer Treatment Protocols”[Title/Abstract]) OR “Cancer Treatment Protocol”[Title/Abstract]) OR Medical Oncology[MeSH Terms]) OR Medical Oncology[Title/Abstract]) OR “Clinical Oncology”[Title/Abstract]) OR Drug Therapy[MeSH Terms]) OR Drug Therapy[Title/Abstract]) OR “Therapy, Drug”[Title/Abstract]) OR “Drug Therapies”[Title/Abstract]) OR “Therapies, Drug”[Title/Abstract]) OR Chemotherapy[Title/Abstract]) OR Chemotherapies[Title/Abstract]) OR Pharmacotherapy[Title/Abstract]) OR Pharmacotherapies[Title/Abstract]) OR Radiotherapy[MeSH Terms]) OR Radiotherapy[Title/Abstract]) OR Radiotherapies[Title/Abstract]) OR “Radiation Therapy”[Title/Abstract]) OR “Radiation Therapies”[Title/Abstract]) OR “Radiation Treatment”[Title/Abstract]) OR “Radiation Treatments”[Title/Abstract]) OR “Targeted Radiotherapies”[Title/Abstract]) OR “Targeted Radiotherapy”[Title/Abstract]) OR “Targeted Radiation Therapy”[Title/Abstract]) OR “Targeted Radiation Therapies”[Title/Abstract]))) AND ((((((Stomatitis[MeSH Terms]) OR Stomatitis[Title/Abstract]) OR Stomatitides[Title/Abstract]) OR “Oral Mucositis”[Title/Abstract]) OR Oromucositis[Title/Abstract]))) AND (((((((length of stay[MeSH Terms]) OR length of stay[Title/Abstract]) OR “Stay Length”[Title/Abstract]) OR “Stay Lengths”[Title/Abstract]) OR “Hospital Stay”[Title/Abstract]) OR “Hospital Stays”[Title/Abstract]))
Scopus	((infant OR infants OR "Child, Preschool" OR "Preschool Child" OR "Preschool Children" OR child OR children OR adolescent OR adolescents OR adolescence OR teens OR teen OR teenagers OR teenager OR youth OR youths OR "Female Adolescent" OR "Female Adolescents" OR "Male Adolescent" OR "Male Adolescents" OR "Antineoplastic Protocol" OR "Protocols, Antineoplastic" OR "Antineoplastic Protocols" OR "Cancer Treatment Protocols" OR "Cancer Treatment Protocol" OR "Medical Oncology" OR "Clinical Oncology" OR "Drug Therapy" OR "Therapy, Drug" OR "Drug Therapies" OR "Therapies, Drug" OR chemotherapy OR chemotherapies OR pharmacotherapy OR pharmacotherapies OR radiotherapy OR radiotherapies OR "Radiation Therapy" OR "Radiation Therapies" OR "Radiation Treatment" OR "Radiation Treatments" OR "Targeted Radiotherapies" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy" OR "Targeted Radiation Therapies")) AND ((stomatitis OR stomatitides OR "Oral Mucositis" OR oromucositis)) AND (("length of stay" OR "Stay Length" OR "Stay Lengths" OR "Hospital Stay" OR "Hospital Stays" OR "hospitalization time" OR "hospitalization period"))
Web of Science	TS=(Infant OR Infants OR “Child, Preschool” OR “Preschool Child” OR “Preschool Children” OR Child OR Children OR Adolescent OR Adolescents OR Adolescence OR Teens OR Teen OR Teenagers OR Teenager OR Youth OR Youths OR “Female Adolescent” OR “Female Adolescents” OR “Male Adolescent” OR “Male Adolescents" OR “Antineoplastic Protocol” OR “Protocols, Antineoplastic” OR “Antineoplastic Protocols” OR “Cancer Treatment Protocols” OR “Cancer Treatment Protocol” OR “Medical Oncology” OR “Clinical Oncology” OR “Drug Therapy” OR “Therapy, Drug” OR “Drug Therapies” OR “Therapies, Drug” OR Chemotherapy OR Chemotherapies OR Pharmacotherapy OR Pharmacotherapies OR Radiotherapy OR Radiotherapies

	OR “Radiation Therapy” OR “Radiation Therapies” OR “Radiation Treatment” OR “Radiation Treatments” OR “Targeted Radiotherapies” OR “Targeted Radiotherapy” OR “Targeted Radiation Therapy” OR “Targeted Radiation Therapies”) AND TS=(Stomatitis OR Stomatitides OR “Oral Mucositis” OR Oromucositis) AND TS=(“length of stay” OR “Stay Length” OR “Stay Lengths” OR “Hospital Stay” OR “Hospital Stays” OR "hospitalization time" OR "hospitalization period")

ANEXO 1 - Certidão de aprovação do CEP

UFPB - CENTRO DE CIÊNCIAS DA SAÚDE DA UNIVERSIDADE FEDERAL DA PARAÍBA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE DA RELAÇÃO ENTRE AS CONDIÇÕES DE SAÚDE BUCAL E O TRATAMENTO QUIMIOTERÁPICO EM PACIENTES PEDIÁTRICOS ONCOLÓGICOS ASSISTIDOS EM UM HOSPITAL DE REFERÊNCIA NA CIDADE DE JOÃO

Pesquisador: ISABELLA LIMA ARRAIS RIBEIRO

Área Temática:

Versão: 2

CAAE: 12922113.8.0000.5188

Instituição Proponente: Centro de Ciência da Saúde

Patrocinador Principal: FUND COORD DE APERFEICOAMENTO DE PESSOAL DE NIVEL SUP

DADOS DA NOTIFICAÇÃO

Tipo de Notificação: Outros

Detalhe: Declaração da Instituição onde o projeto foi realizado de que o trabalho final foi

Justificativa: Envio em anexo a declaração de entrega da Versão Final do Trabalho de Tese junto

Data do Envio: 08/11/2016

Situação da Notificação: Parecer Consubstanciado Emitido

DADOS DO PARECER

Número do Parecer: 2.055.711

Apresentação da Notificação:

O projeto de pesquisa em tela tem como título: "ANÁLISE DA RELAÇÃO ENTRE AS CONDIÇÕES DE SAÚDE BUCAL E O TRATAMENTO QUIMIOTERÁPICO EM PACIENTES PEDIÁTRICOS ONCOLÓGICOS ASSISTIDOS EM UM HOSPITAL DE REFERÊNCIA NA CIDADE DE JOÃO PESSOA". Trata-se de uma complementação de dados de um estudo já realizado pela pesquisadora. A presente proposta se caracteriza como sendo um estudo longitudinal, prospectivo, observacional, randomizado, não cego, caracterizando uma Coorte. Os pesquisadores realizarão procedimentos comparativo-estatísticos e técnica de observação direta intensiva por meio da avaliação das condições clínicas orais anteriormente observadas e durante o tratamento quimioterápico antineoplásico. Serão preenchidos formulários e realizadas entrevistas com os pacientes e seus responsáveis estudo. A

Endereço: UNIVERSITARIO S/N
Bairro: CASTELO BRANCO **CEP:** 58.051-900
UF: PB **Município:** JOAO PESSOA
Telefone: (83)3216-7791 **Fax:** (83)3216-7791 **E-mail:** eticaccsufpb@hotmail.com

amostra será composta de 100 participantes e tem financiamento pelo CNPq.

Objetivo da Notificação:

Informar ao CEP e confirmar a entrega do projeto ao centro colaborador. Para tanto, foi e anexada uma declaração nesse sentido.

Avaliação dos Riscos e Benefícios:

Os autores relatam que o presente estudo realizará avaliações das condições de saúde da cavidade oral, mediante inspeção clínica; podendo, a depender da necessidade, serem realizadas intervenções curativas e preventivas minimamente invasivas e ainda aplicações pontuais de laser em lesões ulcerativas, seguindo um protocolo de tratamento e cuidados, com comunicação constante com a equipe médica, oferecendo riscos mínimos aos pacientes incluídos Os benefícios estão relacionados ao monitoramento durante as avaliações e aos novos conhecimentos para um adequado atendimento desse tipo de paciente.

Comentários e Considerações sobre a Notificação:

nada a declarar

Considerações sobre os Termos de apresentação obrigatória:

nada a declarar

Recomendações:

nada a declarar

Conclusões ou Pendências e Lista de Inadequações:

nada a declarar

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	Declaracao_HNL.pdf	08/11/2016 15:11:30	ISABELLA LIMA ARRAIS RIBEIRO	Aceito

Situação do Parecer:

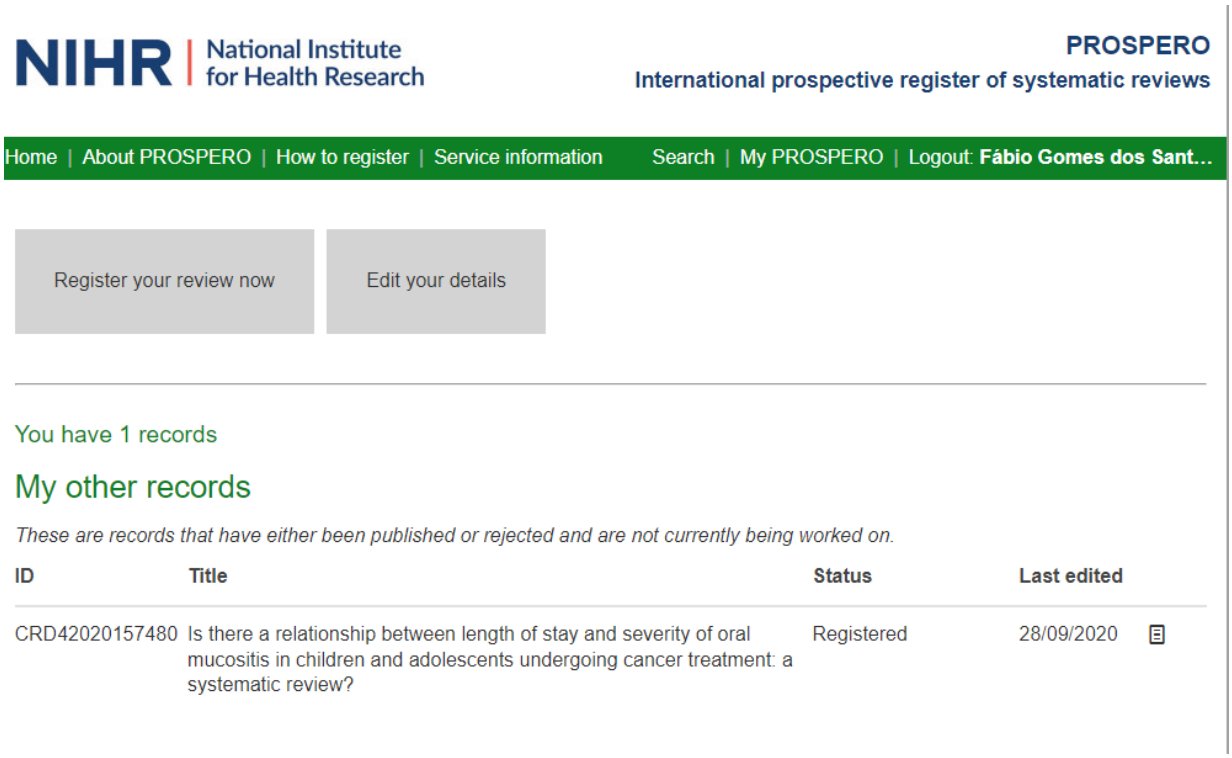
Aprovado

Necessita Apreciação da CONEP:

Não

Endereço: UNIVERSITARIO S/N
Bairro: CASTELO BRANCO **CEP:** 58.051-900
UF: PB **Município:** JOAO PESSOA
Telefone: (83)3216-7791 **Fax:** (83)3216-7791 **E-mail:** eticaccsufpb@hotmail.com

ANEXO 2 – Registro da revisão sistemática no PROSPERO



NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Home | About PROSPERO | How to register | Service information Search | My PROSPERO | Logout: **Fábio Gomes dos Sant...**

Register your review now Edit your details

You have 1 records

My other records

These are records that have either been published or rejected and are not currently being worked on.

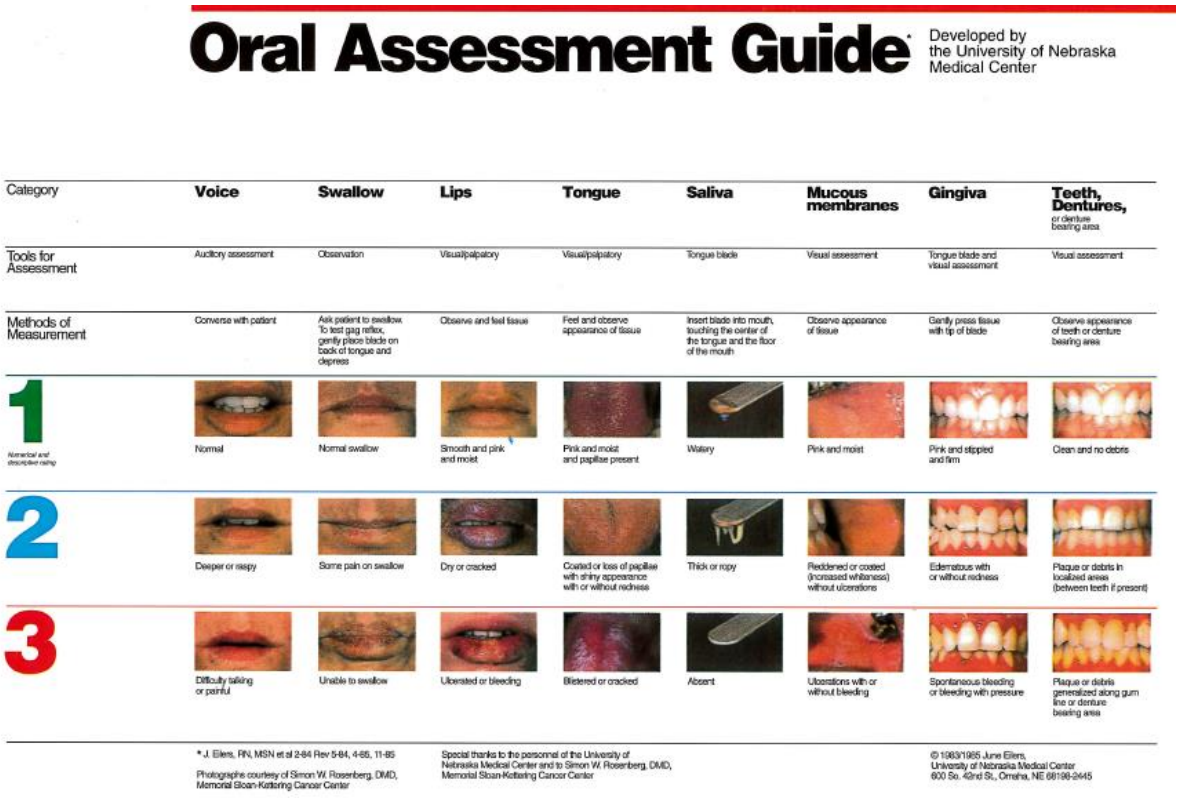
ID	Title	Status	Last edited
CRD42020157480	Is there a relationship between length of stay and severity of oral mucositis in children and adolescents undergoing cancer treatment: a systematic review?	Registered	28/09/2020

ANEXO 3 – Escalas de mensuração da mucosite oral

World Health Organization (WHO) scale

Mucositis grade					
Scale	**0**	**1**	**2**	**3**	**4**
WHO Oral Toxicity Scale	None	*Soreness* and erythema	Erythema, *ulcers*, patient can swallow *solid diet*	*Ulcers*, extensive erythema, patient *cannot swallow solid diet*	Mucositis to extent that *alimentation is not possible*

WHO, World Health Organization.



CHILDREN'S INTERNATIONAL MUCOSITIS EVALUATION SCALE (ChIMES)

PAIN

1. Which of these faces best describes how much pain your child feels in their mouth or throat today? Circle one.

FUNCTION

2. Which of these faces shows how hard it is for your child to SWALLOW their saliva/spit today because of mouth or throat pain? Circle one.

3. Which of these faces shows how hard it is for your child to EAT today because of mouth or throat pain? Circle one.

4. Which of these faces shows how hard it is for your child to DRINK today because of mouth or throat pain? Circle one.

PAIN MEDICATION

5. Has your child taken medicine for any kind of pain today?

☐ Yes ☐ No

If yes, did your child need the medicine because they had mouth or throat pain?

☐ Yes ☐ No

APPEARANCE

6. Please look in your child's mouth. Can you see any mouth sores (ulcers)?

☐ Yes ☐ No ☐ Can't tell

Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal.					
Navigational Note: -					

Oral Mucositis Assessment Scale

TABLE 1
Sample Data Collection Form Indicating the Parameters and Sites for the Objective Scoring Used for Chemotherapy Patients

Chemotherapy

Patient ID

_____ _____ /_____1_____ /_____ _____
site regimen pt. #

Patient Initials

_____ _____ _____
first middle last

Date: ___ ___ /___ ___ /___ ___
mm dd yy

Time (24 hour clock): ___ ___ : ___ ___

Patient is today: Inpatient Outpatient
(circle)

Investigator 1

Location	Ulceration/pseudomembrane* (circle)				Erythema** (circle)		
Upper lip	0	1	2	3	0	1	2
Lower lip	0	1	2	3	0	1	2
Right cheek	0	1	2	3	0	1	2
Left cheek	0	1	2	3	0	1	2
Right ventral and lateral tongue	0	1	2	3	0	1	2
Left ventral and lateral tongue	0	1	2	3	0	1	2
Floor of mouth	0	1	2	3	0	1	2
Soft palate/fauces	0	1	2	3	0	1	2
Hard palate	0	1	2	3	0	1	2

*Ulceration/Pseudomembrane:
0 = no lesion
1 = < 1 cm^2
2 = 1 cm^2–3 cm^2
3 = > 3 cm^2

**Erythema:
0 = none
1 = not severe
2 = severe

NCI grade
WBC (μ^3)
ANC (μ^3)

Presence of infection: Yes No (circle) If yes, circle: local non-oral systemic

Investigator's Signature: _____

NCI: National Cancer Institute; WBC: leukocyte; ANC: absolute neutrophil count.
The same data were collected for patients receiving radiation therapy, although absolute neutrophil count was omitted.

OMDQ: ORAL MUCOSITIS DAILY QUESTIONNAIRE

To be administered at baseline and daily thereafter BEFORE all clinical oral mucositis assessments throughout the oral mucositis evaluation period for cycles 1 and 2.

1. How would you rate your OVERALL HEALTH during the PAST 24 HOURS? Please circle the most appropriate number.

0	1	2	3	4	5	6	7	8	9	10
Worst possible										Perfect Health

2. During the PAST 24 HOURS, how much **MOUTH AND THROAT SORENESS** did you have? *(Circle one number)*

No soreness	0
A little soreness	1
Moderate soreness	2
Quite a lot of soreness	3
Extreme soreness	4

3. During the PAST 24 HOURS, how much did **MOUTH AND THROAT SORENESS** limit you in each of the following activities? *(Circle one number on each line)*

	Not Limited	Limited A Little	Limited Some	Limited A Lot	Unable To Do
a. Sleeping	0	1	2	3	4
b. Swallowing	0	1	2	3	4
c. Drinking	0	1	2	3	4
d. Eating	0	1	2	3	4
e. Talking	0	1	2	3	4

4. On a scale from 0 to 10, how would you rate your **OVERALL MOUTH AND THROAT SORENESS** during the PAST 24 HOURS?
Please circle the most appropriate number.

0	1	2	3	4	5	6	7	8	9	10
No Soreness										Worst Possible Soreness

If you have had a colostomy, please skip to question 6

5a. During the PAST 24 HOURS, how many **BOWEL MOVEMENTS** did you have?
(Please enter the number in the box)

5b. If you had a bowel movement during the past 24 hours, how would you best describe your stools?

Normal	0
Hard or lumpy	1
Loose or watery	2
Bloody	3
Passing mucus (white material) during bowel movement	4

If you have NOT had a colostomy, please stop here

When your chemotherapy treatment begins, you will be asked to compare your ostomy output to what it was before your treatment began. Please try to compare the ostomy output you have during your treatment to the ostomy output you currently have prior to the start of your chemotherapy treatment.

6. Have you had an increase in ostomy output during the PAST 24 HOURS?
Yes No
(Please circle yes or no)

How would you rate your increase in ostomy output compared to before your chemotherapy began?
(Please circle the most appropriate number)

No increase	0
Mild increase	1
Moderate increase	2
Severe increase	3

ANEXO 4 – *Checklist* STROBE

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page/Lines
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p.59
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p.59
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p.61
Objectives	3	State specific objectives, including any prespecified hypotheses	p.61/lines 29-40
Methods			
Study design	4	Present key elements of study design early in the paper	p.62/lines 46-56
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p.62/lines 60-64
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p.63/lines 68-76
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.63/lines 80-94
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p.63-64/lines 98-124
Bias	9	Describe any efforts to address potential sources of bias	p.64/lines 103-112
Study size	10	Explain how the study size was arrived at	p.63/lines 76-77
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p.63/lines 80-94
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p.64-65
		(*b*) Describe any methods used to examine subgroups and interactions	p.64-65
		(*c*) Explain how missing data were addressed	not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	not applicable
		(*e*) Describe any sensitivity analyses	not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p.65/lines 159-162.
		(b) Give reasons for non-participation at each stage	p.65/lines 159-162.
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	p.65-66/ lines

		clinical, social) and information on exposures and potential confounders	162-170
		(b) Indicate number of participants with missing data for each variable of interest	not applicable
		(c) Summarise follow-up time (eg, average and total amount)	p.66
Outcome data	15*	Report numbers of outcome events or summary measures over time	p.66-67
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 and 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	p.67/lines 219-230
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p.72
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p.67-72
Generalisability	21	Discuss the generalisability (external validity) of the study results	p.67-72
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.73

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.