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JÚLIA BREDA SOARES

ESCALAS DE AVALIAÇÃO DA MUCOSITE ORAL EM PACIENTES ONCOLÓGICOS PEDIÁTRICOS: UMA REVISÃO SISTEMÁTICA

Porto Alegre
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Dissertação de mestrado apresentada ao Programa de Pós-graduação em Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para obtenção do título de Mestre em Odontologia.

Orientador: Manoela Domingues Martins

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Porto Alegre, 15 de março de 2024.

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RESUMO

SOARES, Julia Breda. **ESCALAS DE AVALIAÇÃO DA MUCOSITE ORAL EM PACIENTES ONCOLÓGICOS PEDIÁTRICOS E ADOLESCENTES: UMA REVISÃO SISTEMÁTICA.** 2023. Dissertação (Pós-graduação em Clínica Odontológica com ênfase em Estomatologia) – Faculdade de Odontologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, 2023.

O câncer infantil representa cerca de 8% do total de mortes entre crianças e adolescentes no Brasil, e pode envolver diferentes modalidades terapêuticas como cirurgia, radioterapia (RT) e quimioterapia (QT). Diversos efeitos adversos orais debilitantes podem estar associados ao uso dos quimioterápicos e a RT de cabeça e pescoço, entre elas está a mucosite oral (MO), que é uma reação tóxica inflamatória da mucosa oral. A avaliação da MO é muito importante na tomada de decisões clínicas, promovendo o melhor manejo e tratamento para os pacientes. Porém, a escala de classificação das lesões em crianças atualmente não é tão consolidada quanto em adultos. Na pesquisa clínica, a padronização dessas avaliações é essencial para o desenvolvimento de estudos intervencionais que visam avaliar a eficácia de diferentes protocolos para prevenção e tratamento da MO. O objetivo do estudo foi realizar uma revisão sistemática sobre avaliar as ferramentas que vêm sendo utilizadas para classificar a MO em pacientes oncológicos pediátricos e adolescentes. Metodologia: Este estudo seguiu as diretrizes de Itens de Relatório Preferenciais para Revisões Sistemáticas e Meta-análises (PRISMA). A estratégia de busca foi realizada nas seguintes bases de dados no MEDLINE/PubMed, EMBASE, Web of Science e Scopus. Resultado: Foram incluídos 110 artigos. Ao todo, foram avaliados 7.713 pacientes pediátricos, sendo 50.9% meninos e 36.6% meninas. A idade variou de 0 a 19 anos. Do total de 110 estudos, 49% envolveram pacientes em tratamento para neoplasias hematológicas (HM) ou tumores sólidos (ST) e 45,4% dos estudos foram apenas com pacientes com HM. A escala de MO da OMS é a mais utilizada, embora não considere critérios específicos para pacientes pediátricos e foi descrita em 63.6% dos estudos. A OAG foi utilizada em 15.4% dos estudos e Children's International Mucosite Evaluation Scale (ChIMES) em 8.1% dos estudos. Conclusão: A pouca quantidade de instrumentos validados para avaliação da MO em pacientes pediátricos pode levar ao uso inadequado de escalas feitas para adultos. Escalas específicas para pacientes pediátricos, como o ChIMES, devem ser indicadas para facilitar a avaliação nesses pacientes.

Palavras-chave: Mucosite oral; Pediátrico; Escala de Mucosite;

ABSTRACT

SOARES, Julia Breda. **ORAL MUCOSITIS ASSESSMENT IN PEDIATRIC AND ADOLESCENT ONCOLOGICAL PATIENTS: A SYSTEMATIC REVIEW** 2023. Dissertation (Postgraduate in Dentistry, Dental Clinics - Stomatology) – School of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, 2024

Childhood cancer represents about 8% of total deaths among children and adolescents in Brazil, and can involve different therapeutic modalities such as surgery, radiotherapy (RT) and chemotherapy (CT). Several debilitating adverse oral effects may be associated with the use of chemotherapy drugs and head and neck RT, including oral mucositis (OM), which is an inflammatory toxic event of the oral mucosa. OM assessment is very important in clinical decision-making, promoting the best management and treatment for patients. However, the classification scale for injuries in children is currently not as consolidated as in adults. In clinical research, the standardization of these assessments is essential for the development of interventional studies that aim to evaluate the effectiveness of different protocols for the prevention and treatment of OM. The objective of the study was to carry out a systematic review to evaluate the tools that have been used to classify OM in pediatric and adolescent oncology patients. Methodology: This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy was carried out in the following databases: MEDLINE/PubMed, EMBASE, Web of Science and Scopus. Result: 110 articles were included. In total, 7,713 pediatric patients were evaluated, 50.9% boys and 36.6% girls. Ages range from 0 to 19 years old. Of the total of 110 studies, 49% involved patients undergoing treatment for hematological malignancies (HM) or solid tumors (ST) and 45.4% of the studies were only with patients with MH. The WHO OM scale is the most used, although it does not consider specific criteria for pediatric patients and was described in 63.6% of studies. The OAG was used in 15.4% of the studies and the Children's International Mucositis Evaluation Scale (ChIMES) in 8.1% of the studies. Conclusion: The small number of validated instruments for assessing OM in pediatric patients may lead to the inappropriate use of scales designed for adults. Specific scales for pediatric patients, such as ChIMES, should be indicated to facilitate the assessment of these patients.

Keywords: Oral Mucositis; Pediatric; Mucositis Scale;

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LISTA DE ABREVIATURAS E SIGLAS

AMPs	Nucleotídeos Adenosina Monofosfato
ChIMES	Children's International Mucositis Evaluation Scale
DNA	Ácido Desoxirribonucleico
ECOG	Eastern Cooperative Oncology Group
ERO	Espécies Reativas de Oxigênio
EVA	Escala Visual Analógica
MO	Mucosite Oral
MMPs	Metaloproteinases de matriz
MTX	Metotrexato
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF-Kb	Fator nuclear kappa-B
OAG	Oral Assessment Guide
OMAS	Oral Mucositis Assessment Scale
OMS	Organização Mundial da Saúde
OMDQ	Questionário da Avaliação da Mucosite Oral diária
PAMPs	Pathogen-associated molecular pattern
PROMs	Patient reported outcome measures
QT	Quimioterapia
RT	Radioterapia
RT-CP	Radioterapia nas regiões de cabeça e pescoço
RTOG	Radiation Therapy Oncology Group
TCPH	Transplante de Células Progenitoras Hematopoiéticas

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1 INTRODUÇÃO

O câncer representa um dos principais desafios de saúde pública enfrentado globalmente, tendo um impacto na qualidade de vida e na sobrevida dos pacientes (De Martel, 2020; INCA, 2022; WHO, 2022). No Brasil, o câncer é a principal causa de morte por doenças entre crianças e adolescentes. Estima-se que haverá cerca de 7.290 novos casos de câncer infantojuvenil no país até o ano de 2040, representando uma redução de 14,6% em comparação com as projeções feitas em 2022. Mundialmente, até o ano de 2040 277.000 novos casos de câncer infantojuvenil são estimados. (Globocan, 2020; INCA, 2022). As neoplasias malignas mais comuns em crianças incluem a leucemia linfoblástica aguda, leucemia mieloide aguda, linfomas e tumores que afetam o sistema nervoso central. Além disso, tumores de Wilms, osteossarcomas e retinoblastomas são doenças frequentemente diagnosticadas em crianças e adolescentes (INCA, 2022; Ward et al., 2019).

O tratamento de câncer é altamente personalizado e depende das características individuais do paciente, da neoplasia e estadiamento do câncer, podendo envolver diferentes modalidades terapêuticas como cirurgia, radioterapia (RT), quimioterapia (QT), imunoterapia, terapia alvo, terapia hormonal e transplante de células progenitoras hematopoiéticas (TCPH) (INCA, 2022, Kamrani et al., 2023). Frequentemente, uma combinação de tratamentos é utilizada para alcançar os melhores resultados. Além disso, o bem-estar físico, psicossocial e espiritual do paciente deve ser priorizado, com o apoio de equipes multidisciplinares (WHO, 2022).

A quimioterapia é considerada a principal abordagem no tratamento oncológico do paciente pediátrico e adolescente visando direcionar suas ações para erradicar as células tumorais, que têm uma elevada taxa de divisão celular. No entanto, devido à falta de especificidade, também podem afetar células saudáveis (Blijham, 1993; Bonassa, 2023). Os medicamentos quimioterápicos mais comuns usados no tratamento de câncer neste grupo de

pacientes incluem o metotrexato (MTX), vincristina, doxorrubicina (ou adriamicina), ciclofosfamida, cisplatina, etoposídeo e ifosfamida (De Farias Gabriel et al., 2022). Esses medicamentos quimioterápicos são frequentemente administrados em regimes de tratamento combinados e os protocolos podem variar ao longo do tempo. Diversos efeitos adversos podem estar associados ao seu uso, como mucosite oral (MO), náuseas, diarreia, toxicidade hepática e renal, e dermatites (Bonassa, 2023; NCI, 2019). Quando utilizada, a RT nas regiões de cabeça e pescoço (RT-CP) pode causar efeitos adversos como MO, osteorradionecrose, cáries de radiação, disfagia, xerostomia entre outros (NCI, 2019).

A MO é o efeito adverso agudo mais comumente observado em pacientes submetidos a QT e RT-CP (Morais-faria et al., 2020; Kauark-fontes et al., 2022). Sua prevalência em casos de tratamento com QT, no geral, varia de 30% a 75% (Aggarwal et al., 2014; Dodd et al., 2000)**.** Já nos casos de tratamento com RT-CP, cerca de 80% a 100% dos pacientes acabam desenvolvendo MO (Trotti et al., 2003; Scully et al., 2003; Antunes 2013). Em relação à população pediátrica com câncer, a chance de desenvolvimento de MO é três vezes maior quando comparado com pacientes oncológicos adultos. O acometimento da população oncopediátrica varia de 15% a 99% e isso se deve aos altos índices de mitoses durante o período de crescimento tornando o epitélio bucal mais suscetível ao dano da RT e QT (Bulut; Tüfekci, 2016; Cacceli; Pereira; Rapoport, 2009; Soares et al., 2011; Yavuz; Bal Y Lmaz, 2014; Jehmilich et al., 2015) No grupo pediátrico, a idade pode influenciar na prevalência da MO, onde pacientes menores de 12 anos têm a possibilidade aumentada de desenvolver esta complicação (Childers et al., 1993; Devi et al., 2013). Possivelmente, isso ocorre em decorrência das particularidades do sistema imunológico em fase de desenvolvimento e da imaturidade das estruturas bucais, os quais desempenham papéis secundários nos potenciais riscos associados ao aumento na incidência e gravidade de complicações orais decorrentes do tratamento antineoplásico (Morais et al., 2014).

Crianças com leucemias ou linfomas avançados normalmente recebem tratamentos mais agressivos, e consequentemente estão mais suscetíveis a desenvolver a MO, assim como as crianças que realizam TCPH (Cheng et al., 2008; Druley et al., 2009; Figliolia el al., 2008). Dentre os protocolos de QT, alguns são considerados de maior risco para desenvolvimento de MO em pacientes pediátricos dentre os quais os que utilizam MTX em alta dose, daunorrubicina, doxorrubicina, vincristina, etoposídeo, busulfano e citarabina (Elad et al. 2022, Suresh et al., 2019; Khaw et al., 2014; Curra et al., 2018; De Farias et al., 2022).

Outros fatores de risco para MO no grupo pediátrico ressaltados na revisão de Elad et al. (2022) são o baixo peso corporal, níveis de ansiedade, náuseas/vômitos e histórico prévio de MO. A associação entre MO e leucopenia, neutropenia, bem como entre linfopenia em pacientes com tumores sólidos também vem sendo relatados (De Farias Gabriel et al., 2022, Mendonça et al., 2015, Elad et al. 2022). Há evidências conflitantes em relação à associação entre níveis plaquetários e MO (De Farias Gabriel et al., 2022, Bektas-Kayhan et al., *2012,* Elad et al. 2022,). Outros fatores como variantes gênicas, saúde bucal prévia ao tratamento antineoplásico, e a diversificada microbiota oral também merecem atenção quando se trata de risco para MO (De Farias Gabriel et al., 2022).

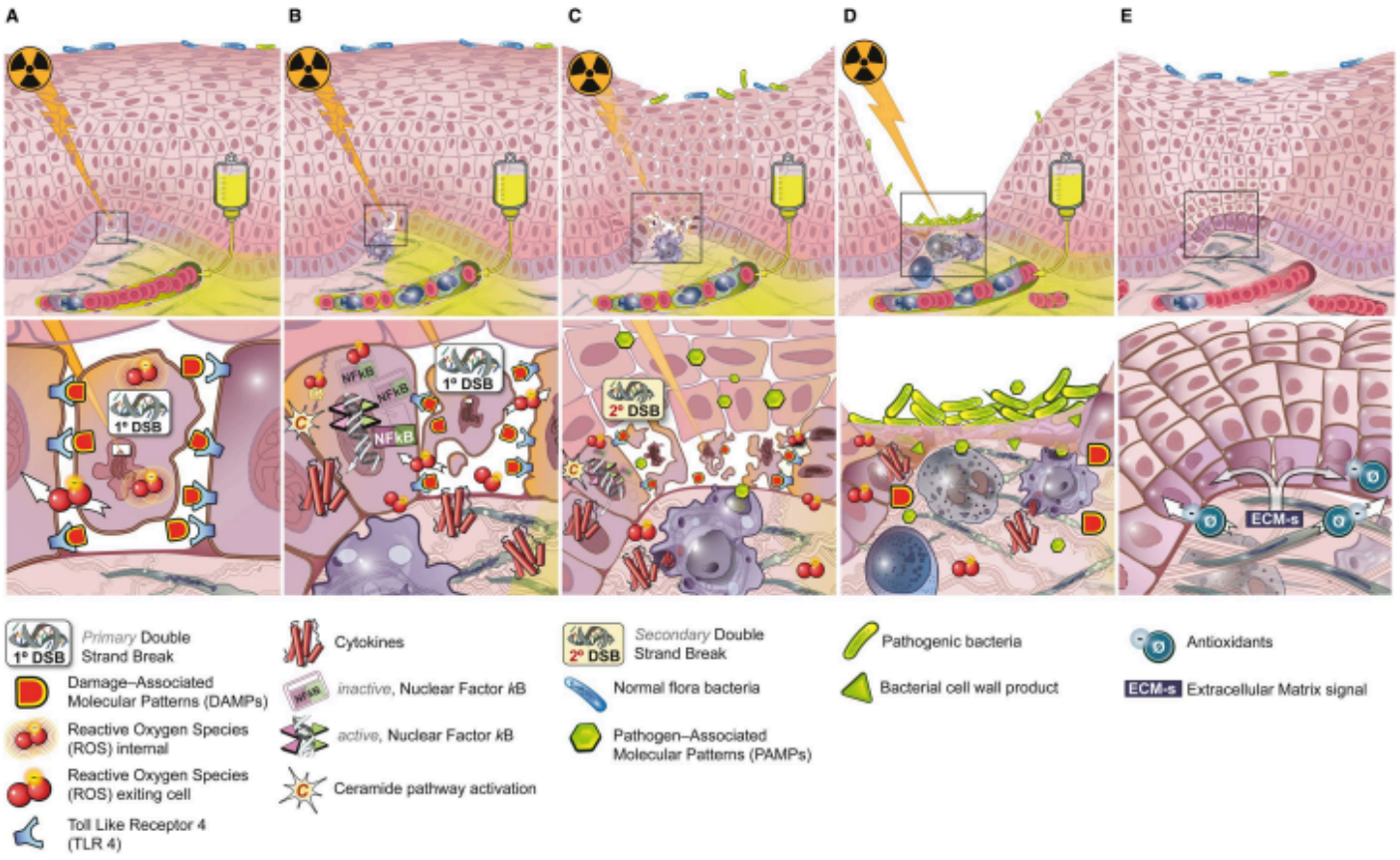
Clinicamente, a MO se apresenta como uma reação inflamatória aguda que pode se manifestar desde pequenas áreas de descamação observadas clinicamente como áreas brancas, até lesões eritematosas e/ou ulceradas de sintomatologia dolorosa significativa (Sonis, 2009; Hurrel et al., 2019). As áreas anatômicas mais frequentemente afetadas são as regiões da mucosa jugal, dorso e borda de língua, assoalho de boca e palato mole (Villa & Sonis, 2020). A sintomatologia das lesões severas de MO pode afetar negativamente o estado nutricional do paciente pois pode impedir a ingestão de alimentos sólidos e líquidos. Além disso, em decorrência do rompimento da mucosa e a quebra das defesas do organismo, infecções oportunistas podem ser observadas (Ariyawardana et al., 2019; Sonis 2011; Bonomo et al.,

2021; Treister et al., 2017, Villa & Sonis, 2020). Nos casos mais severos de MO os pacientes exibem extensas ulcerações associadas a dor o que gera a necessidade de uso de opioides, bem como de antibióticos para prevenir infecções, necessidade de suporte nutricional e outros tratamentos de suporte, bem como, aumento do tempo de hospitalização, modificação ou interrupção do tratamento antineoplásico podendo afetar o prognóstico da doença (Curra et al., 2018; Elad et al., 2022; González-Arriagada et al., 2023; Elting et al., 2003; Rodrigues-Oliveira et al., 2021). Todos esses custos de tratamento somam-se aos gastos com o tratamento primário do câncer e fazem com que a MO eleve os custos do tratamento oncológico (Kauark-Fontes et al., 2023; Rodrigues-Oliveira et al., 2021)

A patogênese da MO é complexa e didaticamente organizada numa sequência de cinco fases (Figura 1). A primeira é a fase de iniciação, onde a RT e/ ou a QT causam dano ao DNA das células, mediado pela produção de espécies reativas de oxigênio (ERO) e pela ativação da resposta imune inata, causando uma cascata de eventos biológicos e imunológicos e que geram apoptose e necrose das células-tronco basais do epitélio e dano ao tecido conjuntivo. Na segunda fase denominada de fase de regulação positiva e ativação, tanto as EROs quanto os nucleotídeos adenosina monofosfato (do inglês *adenosine 3',5'-monophosphate – AMPs*) se ligam aos receptores Toll-Like, como o TLR-4 e ativam os principais fatores de transcrição, como o fator nuclear κB ou NF-κB (do inglês *nuclear factor-κB*). O resultado é produção de citocinas pró-inflamatórias e moléculas sinalizadoras. Ao mesmo tempo, a via da ceramida é ativada após a lipoperoxidação da membrana celular. Enzimas proteolíticas (metaloproteinases de matriz-MMPs) são liberadas e alteram o tecido conjuntivo. Na terceira fase, denominada de amplificação do sinal, o número de moléculas sinalizadoras aumenta causando consequentemente eritema e edema clinicamente na mucosa oral. Os mecanismos de defesa que ocorrem naturalmente, como o controle do estresse oxidativo por enzimas antioxidantes, são sobrecarregados. O aumento da permeabilidade epitelial resultante da

ruptura da junção estreita fornece um canal para os produtos da parede celular das bactérias de superfície denominadas de padrões moleculares associados a patógenos ou PAMPs (do inglês Pathogen-associated molecular pattern) que seguem ativando o sistema imune inato mantendo o dano biológico. Na fase de ulceração, sem reposição, o epitélio se torna atrófico e, por fim, forma-se a úlcera. As bactérias colonizadoras continuam a liberar PAMPs, as enzimas que danificam o tecido continuam a afetar o tecido conjuntivo e são observadas alterações na composição do infiltrado celular. Na fase de cicatrização (fase final), após o término do desafio citotóxico (sem radiação ou quimioterapia adicional), ocorre a cicatrização espontânea, com mensagens da submucosa estimulando a proliferação epitelial e orientando a diferenciação. (Sonis, 1998, 2004, Elad et al., 2022)

Figura 1: A patogênese de MO vem sendo descrita em 5 fases: (A) Iniciação, (B) Regulação positiva e ativação (C) Amplificação (D) Ulceração (E) Cicatrização.



Fonte: Elad et al 2022.

A classificação clínica adequada da MO é essencial para que os profissionais de saúde possam avaliar a sua gravidade e monitorar a condição ao longo do tempo de forma precisa, o que impacta no grau de intervenção necessário (Kennedy e Diamond 1997; Brown e Wingard 2004; Scully et al, 2006; Tomlinson et al, 2007; Vagliano et al, 2011). Por exemplo, pacientes com formas leves de MO podem exigir apenas medidas de suporte e controle da dor, enquanto casos mais graves podem necessitar de intervenções mais complexas, como a suspensão temporária da QT ou redução das doses (Bochud et al., 1994; Sonis 2001, 2004; Kauark-Fontes et al., 2021, 2023; Villa e Sonis 2015; Belim et al., 2002; De Farias Gabriel et al., 2022). As classificações também facilitam a comunicação entre os membros da equipe de saúde, o que é fundamental para garantir que todos estejam cientes da gravidade da condição e das ações a serem tomadas (Cheng et al., 2002; Chen et al., 2004; Aquino et al., 2005; Sung et al., 2017; Tomlinson et al., 2014). Além disso, as classificações permitem que pesquisadores avaliem a eficácia de diferentes intervenções no tratamento da MO e desenvolvam novas estratégias terapêuticas. Em resumo, a classificação adequada da MO desempenha um papel fundamental no manejo eficaz e personalizado dessa condição (Sonis, 2013; Tomlinson et al., 2007, 2008 Tomlinson et al., 2009; Sung et al., 2017).

Existem várias escalas disponíveis para a classificação da MO, e a escolha da escala pode depender das preferências e práticas do profissional de saúde e da população de pacientes atendidos (Jaroneski 2006; Brown e Wingard 2004; McGuire, 2003; Avritscher et al., 2004; Cella et al., 2003; *Attina et al., 2021; Elad et al. 2022*). As escalas usadas com frequência estão detalhadas na Tabela 1.

A escala da Organização Mundial da Saúde (OMS) é usada rotineiramente na prática clínica e em estudos clínicos de MO. Essa escala simples, de 5 pontos (Graus 0 a 4), combina

medidas subjetivas e objetivas da MO. Ela leva em consideração a presença de úlceras, dor e impacto na alimentação, portanto, avalia componentes anatômicos, sintomáticos e funcionais da MO (Elad et al., 2022). A Escala de Mucosite Oral do Instituto Nacional do Câncer Americano (do inglês, *National Cancer Institute - NCI*) está dentro dos critérios de terminologia comum para eventos adversos (NCI-CTCAE). Esta representa uma ferramenta amplamente utilizada para avaliar a MO, sendo uma escala de 5 pontos documenta em crianças e adultos, categorizando a MO em uma escala de 0 a 4, considerando a gravidade dos sintomas e o impacto nas atividades diárias (Cella et al., 2003; Jaroneski 2006). As escalas de critérios de efeitos adversos da NCI têm sido atualizadas durante os anos, somando 5 versões. A Escala de MO da Grupo Oncológico Cooperativo do Leste (do inglês, *Eastern Cooperative Oncology Group*- ECOG) é uma variação da escala da NCI e é usada principalmente em adultos e classifica a mucosite em quatro graus, com descrições detalhadas dos sintomas em cada nível (Anderson et al., 1998; Tomlinson et al., 2007).

A escala de toxicidade aguda do Grupo de Radioterapia e Oncologia (do inglês, *Radiation Therapy Oncology Group- RTOG*) tem sido frequentemente usada para avaliar a MO em pacientes submetidos a RT e classifica a MO em uma escala de 0 a 4, com descrições detalhadas dos sintomas em cada grau porém, sem avaliação funcional (Cox et al., 1995 Tomlinson et al., 2007). O guia de avaliação oral (do inglês, *Oral Assessment Guide*- OAG) desenvolvido por Eilers et al. (1998) avalia oito categorias, sendo elas a voz, deglutição, lábios, língua, saliva, mucosa oral, gengiva e dentes ou próteses. Cada categoria é classificada em uma escala de pontos de 1 a 3, onde 3 é o pior cenário (Eilers et al., 1998). Já a Escala de Avaliação de Mucosite Oral (do inglês, *Oral Mucositis Assessment Scale*- OMAS) desenvolvido por Sonis et al. (2001) avalia nove sítios anatômicos, e para cada local, as ulcerações são pontuadas de 0 a 3, de acordo com a extensão das lesões. O eritema é pontuado de 0 a 2 sendo 0 nenhuma alteração de cor, 1 aumento da cor, e 2 cor de sangue fresco. Os

escores de ulceração e eritema são então somados e resultam em um escore local que varia de 0 a 5 (pior escore possível).

Tabela 1. Avaliação de mucosite bucal de acordo com sua severidade utilizando como base as principais escalas.

	GRAU 0	GRAU 1	GRAU 2	GRAU 3	GRAU 4
OMS	Sem sinais ou sintomas.	Eritema sem lesões.	Mucosa ulcerada, alimentação normal.	Úlceras dolorosas, indivíduo que ingere apenas líquidos.	Alimentação é impossível, necessária dieta parenteral.
OAG	---	Sem dor para engolir. Lábios, voz, língua, saliva, membranas mucosas, e gengivas normais.	Voz rouca, dor ao engolir, lábios secos, língua revestida ou com perda de papilas, saliva espessa, mucosa avermelhada, sem ulcerações.	Dificuldade ao falar, incapaz de engolir, lábios e membranas mucosa ulcerados, língua rachada, falta de saliva, sangramento gengival, placa generalizada.	----
OMAS	Sem eritema ou lesões.	Ulceração/formação de pseudomembrana: área superficial cumulativa < 1 cm; Eritema: leve/moderado.	Ulceração/formação de pseudomembrana: área superficial cumulativa de 1 cm e 3 cm; Eritema: grave (cor de sangue claro).	Ulceração/formação de pseudomembrana: área superficial cumulativa > 3 cm.	----
NCI-CTCAE	Sem mucosite.	Úlceras indolores, eritema ou dor leve, ausência de lesões.	Eritema doloroso, edema ou úlceras, mas consegue comer.	Eritema doloroso, edema ou úlceras, necessitando de hidratação intravenosa.	Ulcerações graves, requer nutrição parenteral ou enteral.
RTOG	---	Eritema, pode apresentar dor leve, não necessitando de analgésico.	Reação irregular (<1,5 cm), pode produzir secreção serossanguinolenta inflamatória.	Mucosite fibrinosa confluente (> 1,5 cm, contígua) pode incluir dor intensa que requer medicamentos.	Ulceração, necrose, sangramento.

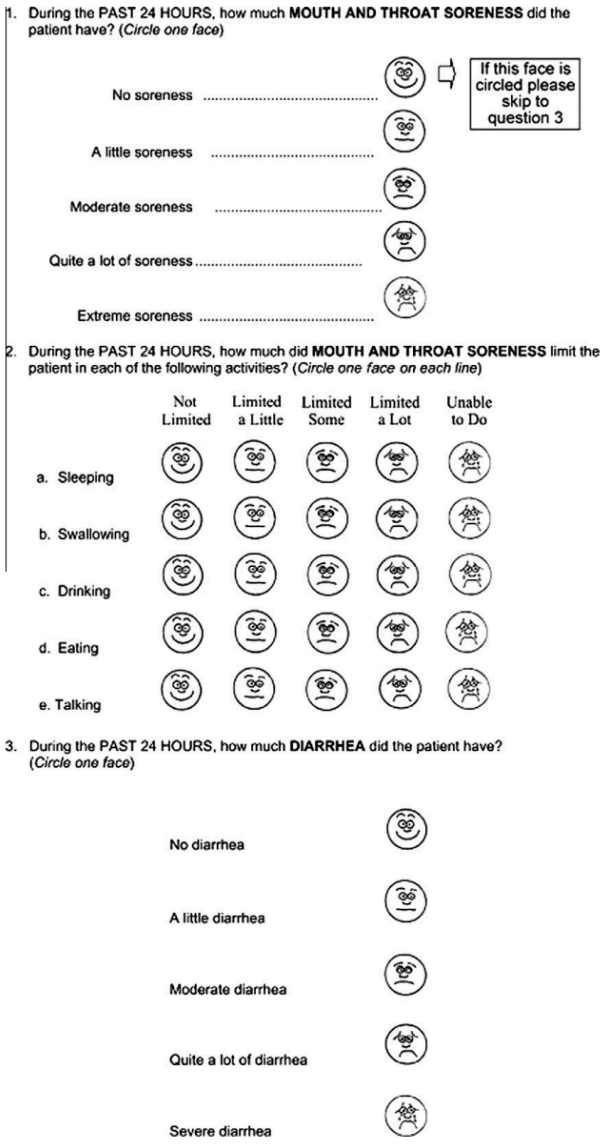
No Questionário de Avaliação da Mucosite Oral diária (do inglês *Oral Mucositis Daily Questionarie*- OMDQ), o paciente relata a sua percepção sobre a sua saúde de uma maneira geral, a presença de diarreia e a intensidade da dor na cavidade oral e orofaringe, e o impacto desta na realização de atividades como engolir, beber, alimentar-se, falar e dormir (Figura 2).

Esse questionário foi validado em populações adultas e pediátricas e é considerado uma ferramenta de medidas de resultados relatadas pelo paciente (do inglês *patient reported outcome measures* - PROMs) (Elad et al., 2022).

As PROMs consideram a perspectiva do paciente, questionando diretamente aos indivíduos sobre seu estado de saúde, sintomas ou experiências. O uso das PROMs destacam a importância de compreender o impacto dos sintomas da MO e como eles são percebidos pelo paciente. Esse tipo de avaliação exige uma padronização confiável, a fim de estimar mudanças e permitir comparações das pontuações do PROM ao longo do tempo (Gutiérrez-Vargas et al., 2016; Franco et al., 2017).

De acordo com Elad et al (2022), documentar a gravidade da MO em crianças pode ser um desafio. Dependendo da idade, a capacidade dos pacientes de compreender as instruções, tolerar o exame da cavidade oral e expressar os sintomas pode exigir a dependência de relatos dos pais. Os mesmos autores afirmam que poucas das escalas de MO mais comuns validadas para adultos foram avaliadas em crianças (Elad et al., 2022).

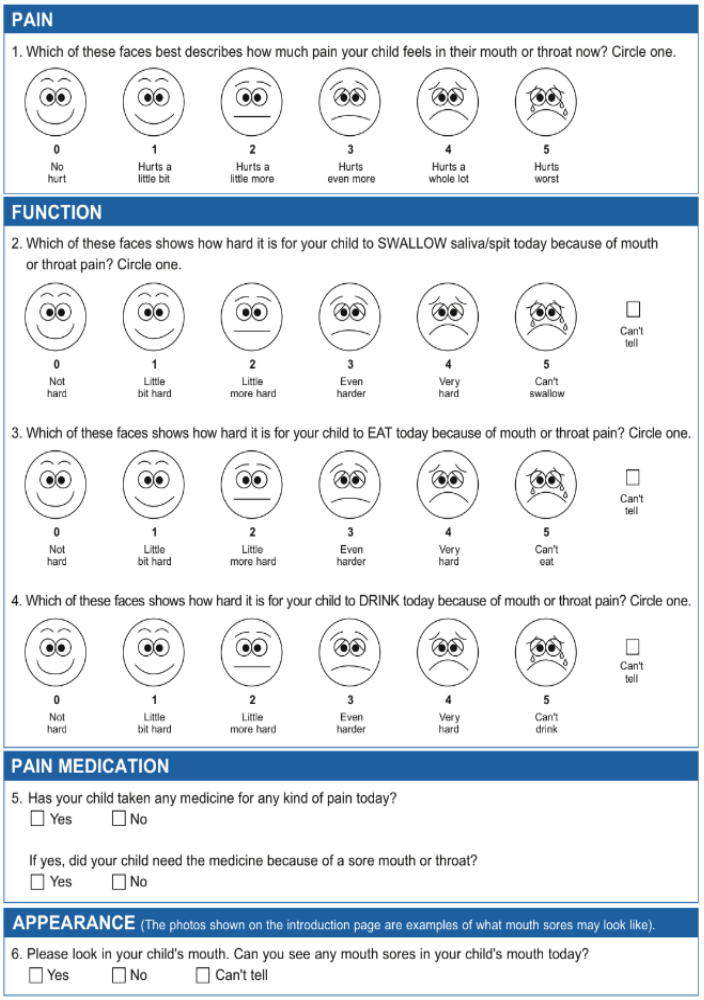
Figura 2. Escala de Avaliação da Mucosite Oral diária



Com o objetivo de minimizar as dificuldades encontradas com a escassez de escalas consolidadas desenvolvidas para a crianças, em 2009 foi criada a Escala Internacional de Avaliação de Mucosite Infantil (Children's International Mucositis Evaluation Scale -ChIMES), feita especificamente para avaliar e classificar a MO em pacientes pediátricos. (Figura 3) (PAIVA et al., 2018; JACOBS et al., 2013). Trata-se de uma escala que contém

uma versão para a criança e uma versão para o responsável. Depois de passar por refinamentos e correções, perguntas sobre a dor, funções, medicamentos para dor e a aparência das lesões passaram a compor a escala. Para facilitar o entendimento, o paciente tem a opção de responder as perguntas através de desenhos de expressões faciais, onde as expressões tristes correspondem ao pior tipo de dor, e as expressões felizes significam a ausência de dor. Diferente das escalas da OMS e da NCI, a ChIMES permite realizar o auto-relato da criança em relação a MO, mas em contrapartida, demonstra-se insuficiente em relação à avaliação clínica das lesões presentes. A pontuação mínima possível dos itens avaliados é 0 e a pontuação máxima possível é 23. (Tomlinson et al., 2009; 2010; Jacobs et al., 2013). Mesmo com a existência de uma escala criada especificamente para crianças, o seu uso ainda não está tão consolidado no dia a dia clínico e em pesquisas tanto quanto outras escalas utilizadas na população adulta. O desenvolvimento de protocolos específicos para avaliação de MO em pacientes pediátricos oncológicos ainda são áreas em crescimento, e diante disto, é necessário o consenso e adaptação dos profissionais de saúde por meio de evidências que demonstrem as melhores opções de escalas, que atendam da melhor forma a população pediátrica, beneficiando o dia a dia clínico e a tomada de decisões por meio de estudos científicos (Tomlinson et al., 2007).

Figura 3. Escala Internacional de Avaliação de Mucosite Infantil- ChIMES



A dor é um sintoma característico, muito comum em pacientes que experienciam a MO. Por esse motivo, estudos indicam a importância da sua avaliação, considerando um desfecho relevante a ser medido em ensaios clínicos Além disso, as escalas de dor também são fundamentais para o melhor manejo do paciente clinicamente, a fim de proporcionar alívio adequado e a melhora da qualidade de vida (Cella et al., 2003).

A Escala Visual Analógica (EVA) é frequentemente usada para avaliar a dor associada à MO, onde o paciente deve marcar a intensidade de sua dor utilizando uma linha reta, onde 0 representa sem dor, e 10 representa a pior dor. Já a escala de Faces de Wong e Baker é projetada para ser intuitiva, sendo considerada de fácil uso para a população infantil. O paciente deve escolher o rosto que melhor representa a intensidade de sua dor, onde o rosto

mais feliz representa a ausência de dor, e as expressões faciais mais tristes representam o maior nível de dor.

A utilização de ferramentas de mensuração desempenha um papel crucial na simplificação da avaliação e na redução da subjetividade inerente às análises da MO Além disso, estabelecem uma uniformidade na linguagem clínica e científica, facilitando o processo diagnóstico. Os instrumentos disponíveis para a avaliação da MO abrangem o uso de escalas objetivas, onde um avaliador treinado observa e documenta as alterações orais, bem como o emprego de escalas que avaliam sintomas subjetivos relacionados à MO, como dor e dificuldade na deglutição. Porém, um dos principais desafios enfrentados na condução de pesquisas sobre a MO reside na escassez de instrumentos de mensuração disponíveis na literatura científica, especialmente para avaliação da população pediátrica.

2. OBJETIVO

2.1 OBJETIVOS GERAIS

Avaliar como a MO tem sido avaliada e classificada em pacientes pediátricos oncológicos.

2.2 OBJETIVOS ESPECÍFICOS

Sugerir um protocolo de avaliação de pacientes pediátricos.

3. ARTIGO CIENTÍFICO

ORAL MUCOSITIS ASSESSMENT IN PEDIATRIC AND ADOLESCENT ONCOLOGICAL PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Oral Mucositis (OM) is a common acute adverse effect of different types of cancer treatments. Its assessment is essential during preventive and treatment strategies. However, the lack of valid pediatric instruments for evaluating OM can provide unreliable data, in addition to creating obstacles for interventional and epidemiological research. **Objective:** The aim of the study was to assess the methods used for evaluating OM in pediatric oncology patients. **Study Design:** The search of this systematic review was performed in MEDLINE/PubMed, EMBASE, Web of Science and Scopus. **Results:** A total of 110 articles were included. Nine different scales were identified. WHO scale was the most utilized, appearing in 63.6% of the studies. Following, the Oral Assessment Guide (OAG) was described in 15.4% of the studies and Common Toxicity Criteria National Cancer Institute (CTC-NCI) was described in 13.6%, while the Children's International Mucositis Evaluation Scale (ChIMES) was used in 8.1% of the studies. In total, 7,713 pediatric patients underwent evaluation, with 50.9% being boys and 36.6% girls. The age ranged from 0-19 years. Among the 110 studies examined, 48.1% included patients undergoing treatment for hematological malignancies (HM) and solid tumors (ST), while 39% focused solely on HM patients. **Conclusion:** Although the WHO scale is commonly used, it does not include specific criteria designed for pediatric patients. It is crucial that the next generation of OM research incorporates validated assessment tools tailored for the young population like ChIMES to improve the OM evaluation.

Keywords: Oral Mucositis; Children; Pediatric; Mucositis Scale; Patient Reported Outcome Measures

Introduction

Oral mucositis (OM) stands out as a significant acute adverse effect among pediatric oncology patients with reported frequencies ranging from 15% to 80.4% (Elad et al., 2020; Curra et al., 2021; Valer et al., 2021; Gabriel et al., 2022). Among children, some risk factors for OM have been described as the type of chemotherapeutic protocol, low body weight, anxiety levels, nausea/vomiting, gene variants, leukopenia, neutropenia and modification in oral microbiota (Mendonca et al., 2015; Vasconcelos et al., 2016; Elad et al., 2022; Gabriel et al., 2022).

Clinically, OM typically manifests as erythema progressing to erosive and/or ulcerative lesions, often accompanied by severe pain. The buccal mucosa, dorsal tongue, floor of the mouth, and soft palate are frequently affected anatomical sites. OM, especially the severe forms can negatively impact the patient's quality of life, affecting the nutritional status of the patients, increasing the prescription of opioids, hospitalization time or even interrupting treatment (Elad et al., 2020; Villa & Sonis, 2020; Reuss et al., 2023).

Numerous tools are available to measure the severity of OM and to support the process of making well-informed treatment decisions by accounting for functional limits, discomfort, and ulceration severity. However, the classification of lesions in children is currently not as consolidated as in adults (Tomlinson et al., 2007; Sung et al. 2007; Tomlinson et al., 2008; Tomlinson et al., 2011; Manji et al. 2012; Elad et al., 2020; Gabriel et al., 2022). Studies indicate that children are at higher risk of developing OM compared with adults, but its assessment can be more problematic due to cooperation and the difficult access, particularly in those who are younger. This lack of valid pediatric instruments may provide unreliable data and inappropriate introduction of costly treatments, in addition to creating obstacles for interventional and epidemiological research (McGuire et al., 2002; Gibson et al., 2006; Tomlinson et al., 2007; Tomlinson et al., 2008; Tomlinson et al., 2009; Glenny et al., 2010; Tomlinson et al., 2014). To the best of our knowledge, no systematic review exploring OM scales in the pediatric population is currently available. In this respect, the objective of this systematic review is how OM and its impact have been evaluated and classified in oncologic pediatric patients.

Materials and Methods

Eligibility criteria

Inclusion criteria

Defined by the PECOS strategy – participants, exposure, comparison, outcomes and type of study –, the inclusion criteria consisted of observational studies, cross sectional studies, case control studies and clinical trials that mention some scale of OM in pediatric patients between 0- and 19-years old undergoing chemotherapy (CT) or head and neck radiotherapy (RT). The searched publications were only considered in the English language, with no restrictions on year of publication.

Exclusion criteria

Review papers, books, duplicate samples, unpublished data, and studies published in languages other than English were excluded.

Information sources and search strategies

Electronic searches were performed without publication date restrictions until October 2023, in the following bibliographic databases: MEDLINE/PubMed, EMBASE, Web of Science and Scopus. Grey literature was searched on Google Scholar and ProQuest. The search strategy was based on nomenclature and synonyms using a combination of MeSH and free terms for *"Oral Mucositis", Children or Pediatric Patients"* and *"Patient Reported Outcome Measures"*. **Appendix 1** shows the search strategy for each database. We also performed manual searches by cross-checking the reference lists of the included studies to identify publications that might have been missed by the primary database searches.

Data collection and variables

Three authors (J.B.S., L.B.K. and A.F.G.) reviewed the titles and abstracts of all studies retrieved. If the title and abstract met the eligibility criteria, the study was included for full-text evaluation. Disagreements between the three authors were referred to a fourth reviewer (M.D.M.) for discussion. Full-text evaluation of the included studies by one author (J.B.S.) resulted in the following extracted data: publication' (author, year and country of publication) and subjects' details (sex, sample, type of cancer, cancer treatment, OM incidence, pain scale, OM scale, characteristics assessed in the scales and patient-reported outcome measures (PROM)).

Risk of bias assessment and critical analysis

We performed a critical appraisal of the included articles using the Joanna Briggs Institute – University of Adelaide tool for cross-sectional studies (Moola et al., 2020). Two

review authors (J.B.S. and A.F.G.) independently performed these judgments based on the criteria for assessing risk of bias. Disagreements were resolved first by discussion and then by consulting a third author for arbitration (L.B.K.).

Other information/Amendments

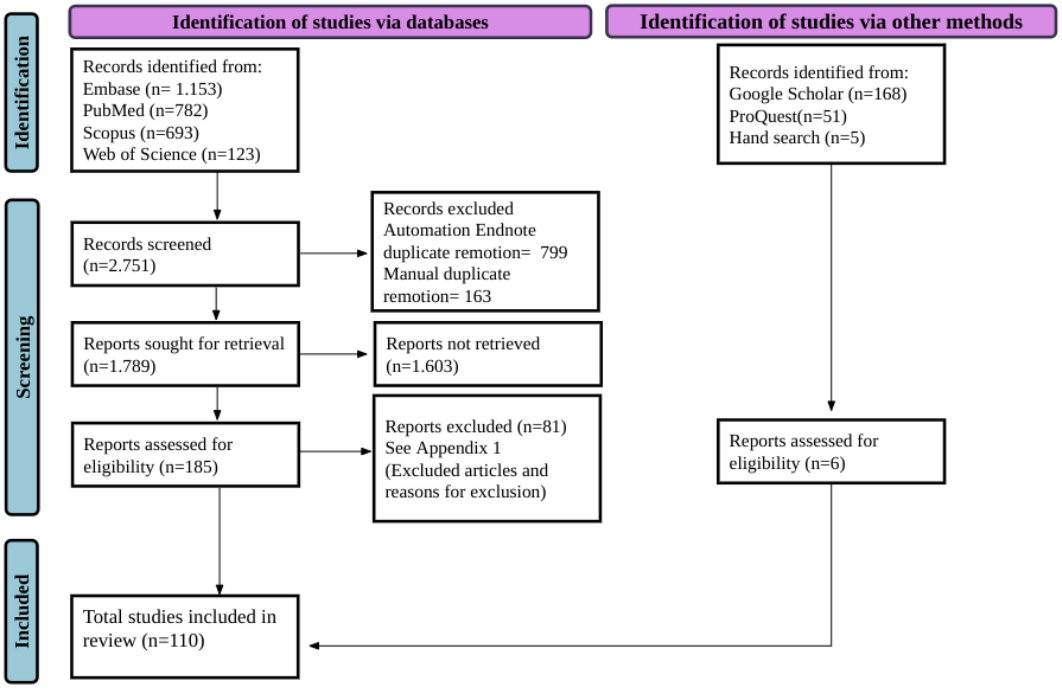
This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al., 2021). A protocol was drafted and registered with the National Institute for Health Research's International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42022333966.

Results

Search results

Figure 1 illustrates the flow of article selection. The literature search screened 2,751 results from the electronic databases. After the exclusion of 962 duplicates, 1,789 titles and abstracts were analyzed, and 185 articles had their full texts assessed for eligibility. Of them, 81 studies were excluded, and the following reasons are outlined in the (**Appendix 2**). Five studies were included from the grey literature search and one study from the hand search. At the end of the systematic search, 110 studies were included in the review (**Appendix 3**).

Figure 1. Flow Chart diagram adapted from PRISMA 2020 (Page et al., 2020).



Studies' characteristics

General and demographic characteristics of the cases of OM included in the present systematic review are summarized in **Table 1** detailed in **Appendix 4**. Most of the studies were published in Brazil (21.8%), followed by Italy (11.8%). All the 110 papers reported together 9 different scales of OM. Cohort studies were the majority (39%), followed by randomized clinical trials (34.5%), quasi experimental studies (13.6%), case control studies (5.4%), cross sectional studies (4.5%) and case report studies (2.7%).

Table 1. General characteristics of the included studies.

Variable	**n (%)**
Continent of publication (n=110)	
Asia	35 (31.8)
America	34 (30.9)
Europe	32 (29.0)
Africa	6 (5.5)
Oceania	3 (2.8)
Sex (n=7,713)	
Male	3,928 (50.9)
Female	2,829 (36.6)
Not informed	956 (12.5)
Ages (n=7,713)	
Range	0-19 years

Cancer Type (n=110)	
Hematological Malignancies or Solid Tumors	54 (49.0%)
Hematological Malignancies	50 (45.4%)
Solid Tumors	2 (1.8%)
Not informed	4 (3.6%)
Treatment (n=110)	
Chemotherapy	94 (85.4%)
Chemotherapy and Radiotherapy	9 (8.1%)
Chemotherapy and Hematopoietic Stem Cell Transplantation	5 (4.5%)
Hematopoietic Stem Cell Transplantation	2 (1.8%)

Subjects' information

All the studies accounted 7,713 oncological patients. Of them, 3,928 males and 2,829 females, 12 studies did not specify the patient's sex. The age ranged from 0 to 19 years, and the mean age ranged from 5 to 13.5. Hematological malignancies or solid tumors were the cancer types seen in 54 studies (49%), followed by only hematological malignancies in 50 studies (45.4%).

Oral Mucositis' Scales and Patient-Related Outcome Measures

The World Health Organization (WHO) Oral Mucositis Scale from 1979 (World Health Organization Handbook for Reporting Results of Cancer Treatment, 1979) were the most used, seen in 70 (63.6%) studies, followed by Oral Assessment Guide (OAG) (Eilers et al., 1988) in 17 (15.4%) studies and Common Toxicity Criteria of National Cancer Institute

(CTC-NCI) in 13 (13.6%) studies (Table 2). Table 3 shows the main differences between the scales used to assess OM in the pediatric patients included in this systematic review.

Only five studies used PROMs, three of them used the Self-report Mouth and Throat Soreness-Related Questions of the Oral Mucositis Daily Questionnaire (OMDQ MTS) (Stiff et al., 2006; Cheng et al., 2011) and two studies questioned the patients' PROMs but did not used a specific questionnaire. Most studies (89.0%) cited only one scale each. Two studies (1.8%) used one OM scale and one PROM, and one study (0.9%) used two scales and one PROM (**Appendix 5**).

Table 2. Frequency of each Oral Mucositis scale.

Oral Mucositis Scale	**N=110 (%)***
World Health Organization (WHO)	**70 (63.6%)**
Oral Assessment Guide (OAG).	**17 (15.4%)**
Common Toxicity Criteria (CTC) National Cancer Institute	**13 (13.6%)**
Children's International Mucositis Evaluation Scale (ChIMES)	**9 (8.1%)**
Modified Oral Assessment Guide (m-OAG)	**5 (4.5%)**
Not nominated scale	**2 (1.8%)**
Oral Mucositis Daily Questionnaire and Oropharyngeal Mucositis Quality of Life Scale (OMQoL)	**1 (0.9%)**
Oral Mucositis Assessment Scale (OMAS)	**1 (0.9%)**
New Mucositis Scoring System drawn by dr. Sonis et al. 1999	**1 (0.9%)**

*One study may have used more than one scale to assess patients' oral mucositis.

Table 3. Differences between the scales used in the included studies of this systematic review

Scale	Grades	Pain assessment	Validation for children	General characteristics
WHO	0 – 4	No	No	**Grade 0,** no signs or symptoms; **Grade 1,** erythema without lesions; **Grade 2,** ulcerated mucosa, but the patient was able to feed normally; **Grade 3,** individual with painful ulcers, individual who ingested only liquids; and **Grade 4,** mucositis to the extent that feeding is impossible, individual who required a parenteral diet.
OAG	1 – 3	No	Yes	Voice, swallowing, lips, tongue, saliva, jugal / palate mucosa, labial mucosa, and gingiva are assessed. **Grade 1,** normal condition; **Grade 2,** mild to moderate alteration in the integrity of the oral epithelium or functional alterations; **Grade 3,** severe impairment.
ChiMES	0 – 5 or 0 – 1	Yes	Yes	**(1)** Amount of mouth or throat pain, **(2)** Effect of mouth or throat pain on swallowing, **(3)** Effect of mouth or throat pain on eating, **(4)** Effect of mouth or throat pain on drinking, **(5)** Receipt of pain medication, **(6)** Receipt of pain medication for mouth or throat pain, and **(7)** Presence of ulcers. 1–4 receive a score of 0–5 where 5 is the worst degree of symptoms. ChIMES 5 received a score of 1 if the child had received pain medications and ChIMES 6 received a score of 1 if the child received pain medications because of mucositis. ChIMES 7 received a score of 1 if oral ulcers were present.
m-OAG	1 – 3	Yes	Yes	**Voice** (**1:** Normal **2:** Deeper or raspy **3:** Difficulty talking or painful) **Swallow** (**1:** Normal swallow **2:** Some pain on swallowing **3:** Unable to swallow) **Lips** (**1:** Smooth and painful and moist **2:** Dry or cracked **3:** Ulcerated bleeding) **Tongue** (**1:** Pink and moist and papillae present, **2:** Coated or loss of papillae with a shiny appearance with or without redness, **3:** Blistered or cracked) **Saliva** (**1:** Watery **2:** Thick or ropy **3:** Absent) **Mucous membrane (buccal mucosa, palate)** (**1:** Pink and moist **2:** Reddened or coated (increased whiteness) without ulceration **3:** Ulceration with or without bleeding) **Mucous membrane (labial mucosa)** (**1:** Pink and moist **2:** Reddened or coated (increased whiteness) without ulceration **3:** Ulceration with or without bleeding) **Gingiva** (**1:** Pink and stippled and firm **2:** Edematous with or without redness **3:** Spontaneous bleeding or bleeding with pressure)
CTC version 2.0	0 – 4	Yes	No	**Grade 0,** without mucositis; **Grade 1,** painless ulcers, erythema, or mild soreness in the absence of lesions; **Grade 2,** painful erythema, edema or ulcers, but able to eat; **Grade 3,** painful erythema, edema or ulcers, requiring intravenous hydration; **Grade 4,** requires parenteral or enteral nutrition or support.

CTC version 3.0	1 – 5	No	No	**Grade 1,** erythema of the mucosa; **Grade 2,** patchy ulcerations or pseudomembranes; **Grade 3,** confluent ulcerations or pseudomembranes; bleeding with minor trauma; **Grade 4,** tissue necrosis, significant spontaneous bleeding, life-threatening consequences; **Grade 5,** death.
CTC version 4.0	1 – 5	No	No	**Grade 1,** asymptomatic or mild symptoms; intervention not indicated. **Grade 2,** moderate pain; not interfering with oral intake; modified diet indicated. **Grade 3,** severe pain; interfering with oral intake. **Grade 4,** life-threatening consequences; urgent intervention indicated. **Grade 5,** death.
OMQoL	1 – 4	Yes	Older than 8 years	31 elements grouped into four dimensions that evaluate the symptomatology, nutrition, social function, and symptomatology for swallowing with a 4-point Likert-type scale (1=not at all; 2=a little; 3=quite a bit; 4=very much).
OMAS	1 – 3 or 0 – 5	No	Older than 6 years	Rating of nine sites (upper/lower lip, right/left inner cheek, right/left ventral and lateral tongue, floor of mouth, soft palate/fauces, and hard palate) For each site, ulceration/pseudomembrane formation is scored from 0 to 3 as follows: **0,** no lesions; **1,** cumulative surface area < 1 cm; **2,** cumulative surface area 1 cm and 3 cm; and **3,** cumulative surface area > 3 cm. Erythema is scored from 0 to 2 as follows: **0,** none (no change in color); **1,** mild/moderate (increase in color); and **2,** severe (color of fresh blood). The ulceration and erythema scores are then summed and result in a site score that ranges from **0(no mucositis) to 5 (worst score possible)**. These nine site ratings then are averaged to result in an overall mucositis score that also ranges from 0 to 5.
Sonis	0 – 3 or 0 – 2	Yes	No	Evaluate ulceration/pseudomembrane (**0**= no lesion; **1**= <1 cm^2; **2**= 1 cm^2 – 3 cm^2; **3**= >3 cm^2) and erythema (**0**= none; **1**= not severe; **2**= severe) of 9 sites of the oral mucosa.

WHO: World Health Organization; OAG: Oral Assessment Guide; m-OAG: Modified Oral Assessment Guide; OMAS: Oral Mucositis Assessment Scale; OMQoL: Oral Mucositis Daily Questionnaire and Oropharyngeal Mucositis Quality of Life Scale; ChiMES: Children's International Mucositis Evaluation Scale; CTC: Common Toxicity Criteria (CTC)

Pain' Scales

From the 110 studies, only 30 (27.2%) used pain scales. Of them, 60% cited the Visual Analog Scale (VAS) (Huskisson, 1974), followed by 13.4% of the studies that used The Faces Scale by Wong and Baker (TFSWB) (Garra et al., 2010) (**Table 4**).

Table 4. Frequency of pain scales in each study.

Pain Scale	**N=30 (27.2%)**
Visual Analog Scale (VAS)	18 (60%)
The Faces Scale by Wong and Baker	4 (13.4%)
NRS scale (numeric pain rating scale)	2 (6.7%)
Faces Pain Scale Revised (FPS-R)	2 (6.7%)
VAS modified with six faces	1 (3.3%)
Smiley faces of the ChIMES scale recording the levels of pain and discomfort	1 (3.3%)
HEDEN	1 (3.3%)
Face Leg Activity Cry Consolability [FLACC] scale	1 (3.3%)

Risk of bias assessment and critical analysis

The risk of bias was assessed for each type of observational and experimental study identified. In cohort studies, most did not identify confounding factors. In randomized clinical trials, many studies were not blinded to the participants, nor to those delivering the treatment. In general, the studies used to analyze adequate statistics (**Appendix 6**).

Discussion

OM is a significant adverse effect in pediatric oncology patients, and its measurement is crucial for planning appropriate preventive and therapeutic activities and the development of new protocols. Various tools exist to gauge its severity and aid in informed treatment decisions, considering functional limitations, discomfort, and ulceration severity. However, compared to adults, the classification of OM lesions in children lacks consolidation. Studies suggest children face a higher risk of OM development but assessing it poses challenges due to cooperation issues and difficult access, especially in younger patients. The absence of reliable pediatric assessment instruments may lead to inaccurate data and unnecessary costly treatments, hindering interventional and epidemiological research. In this context, the present systematic review evaluated 110 studies involving 7,713 pediatric and adolescent oncological patients to assess how OM was evaluated. Our analysis revealed the utilization of nine distinct scales, predominantly WHO and OAG, with limited incorporation of pain scales and PROMS.

The initial tools developed to evaluate oral mucositis (OM) in cancer patients were basic, often employing a scale from 0 (no symptoms) to 5 (severe symptoms). Among the most used simple scales are the WHO and CTC-NCI, which concentrate on the patient's ability to eat and drink, as well as objective indicators of OM (World Health Organization Handbook for Reporting Results of Cancer Treatment, 1979; National Cancer Institute, 2017; Tomlinson et al., 2007). The WHO scale was employed in over 60% of the studies included in this research, often as a standalone tool but occasionally in conjunction with another OM scale. This scale, originally designed for the adult population, categorizes OM into four grades, assessing anatomical sites along with symptomatic and functional components (World Health Organization Handbook for Reporting Results of Cancer Treatment, 1979). Despite its frequent use, the scale lacks validation for pediatric lesion assessment due to various limitations. Complete visualization of the oral cavity is required for accurate grading, posing challenges with uncooperative children (Tomlinson et al., 2007). Moreover, variations in children's eating ability, unrelated to oral lesions, may confound evaluation.

Attention should be given in the assessment of pediatric OM, aspects such as ensure an optimal visualization of the oral cavity and children’s cooperation are important to be considered. Moreover, children’s age is an important limitation in the ability to report subjective and functional items (Tomlinson et al., 2007; Tomlinson et al., 2008). For this reason, the use of an instrument focused on children is extremely important to assess OM in those patients. The scale should be simple and allow a quick and easy response for children. Considering that children have specifical issues when compared to adults, which can reflect in

a better use of a subjective scale instead of an objective one, a multi-disciplinary and multinational group of investigators developed the first draft of ChIMES (Tomlinson et al., 2009), a scale made specifically for children. It is composed of a one version for the child (self-report), and one version adapted to the parents or representatives (parent-proxy), based on the same questions. Face expressions were included in the scale, aiming to facilitate understanding of the children. Doubts in questions about pain medications and the presence of ulcers were reformulated and directed to parents or representatives. Scores for questions about pain or function could range from 0 to 5, and questions about pain medications and appearance of lesions from 0 to 1 from the maximum ChiMES score, which is 23 (Jacobs et al., 2013). This scale was translated and culturally adapted for other languages and had promising results **(**Paiva et al., 2018). On the other hand, we must emphasize that this scale does not evaluate the anatomical sites and the types of the lesions if present. Thus far, there is no single, more precise method of assessing OM in this population, suggesting a combination of the WHO scale (clinical evaluation of the oral mucosa) and CHIMES should be recommended.

Oral pain is an important symptom to be monitored for assessing treatment-related side effects. By closely monitoring oral pain levels, healthcare providers can improve patient outcomes, enhance treatment tolerability, and promote overall well-being in this vulnerable population. However, our results showed that few studies used pain scales during evaluating the clinical presentation of OM (Brown & Wingard, 2004; Zadik et al., 2019). The most used scale in the pediatric oncology population was VAS which is considered reliable and validated only in children older than 8 years old and adults (McGrath et al., 2008). This scale consists of a line measuring 10cm, where the first centimeter represents "no pain" and the last the "worst possible pain" (Huskisson, 1974; Chiarotto et al., 2019). Assessing pain using the VAS in children and adolescents with cancer presents challenges due to their developmental and cognitive differences. It should be considered that children must have a cognitive capacity to translate pain in numbers, as a result the scale can be performed incorrectly. Thus, while the VAS is commonly used in adults, children and adolescents may interpret and respond to pain differently based on their unique psychosocial backgrounds, making it challenging to standardize VAS ratings across diverse pediatric population. Healthcare providers should consider the developmental stage, communication abilities, and individual differences of pediatric patients when interpreting VAS ratings and integrating them into comprehensive pain management strategies. Additionally, employing a multimodal approach to pain

assessment that combines self-report, observation, and caregiver input can enhance the accuracy and reliability of pain assessment in this vulnerable population.

The second most frequently utilized pain scale is TFSWB, recognized as a popular, validated, and user-friendly assessment tool specifically tailored for children. Comprising a series of six cartoon faces depicting various expressions, from a smiling face denoting "no pain" to a tearful face indicating "worst pain," TFSWB offers a simple and intuitive method for pain assessment, particularly suited for pediatric populations. Children are prompted to select the face that best corresponds to their pain level, facilitating easy comprehension due to its subjective representation (Tomlinson et al., 2010). TFSWB proves especially advantageous for children with OM, offering a visual and readily understandable means of expressing pain, even in scenarios where verbal communication may be limited or hindered by oral lesions or treatment-related side effects. In addition to the VAS or TFSWB, it's noteworthy that OM scales incorporate pain assessment within their scores, including ChiMES, m-OAG, CTC-NCI version 2.0, OMQoL, and Dr. Sonis' scale (Tomlinson et al., 2009, Gibson et al., 2006, National Cancer Institute, 1998,, Cheng et al., 2007, Sonis et al., 1999). We advocate for the inclusion of some form of pain evaluation during oncological treatment and oral mucosa analysis of pediatric patients. Despite the potential for bias in pain assessment, given that children may conflate mouth pain with other types of pain, we recommend healthcare providers utilize a pain scale in conjunction with OM evaluation.

In recent decades, healthcare systems have increasingly acknowledged the significance of patients' perspectives in ensuring the delivery of high-quality services that are equitable and safe (Churruca et al.,2021). In this sense, PROMs are considered crucial in the evaluation of oncological patients, offering an all-embracing approach to assessing patient well-being. By capturing subjective experiences such as symptoms, functional status, and quality of life, PROMs provide a comprehensive perspective that complements traditional clinical assessments. They enable the longitudinal tracking of patient outcomes throughout the cancer care continuum, aiding in the identification of unmet needs and areas of concern. Moreover, PROMs support individualized care planning by incorporating patient-reported data into clinical decision-making processes. By prioritizing patients' preferences, goals, and values, personalized care plans can be developed, leading to more patient-centered and tailored interventions (McGee, 2020). Overall, PROMs serve as valuable tools for optimizing patients' quality of life in oncological care (Meryk et al., 2022; Martins et al., 2021; Lopes Martins et al., 2021; Pereira et al., 2018) While regulatory agencies have consistently advocated for the utilization of PROMs in clinical cancer research, their implementation has

predominantly focused on adult patients. Remarkably, few PROMs have been used in oncological pediatric patients (Pereira et al., 2018). Our study agrees with that, since from 110 studies included only five studies used PROMs. OMDQ MTS, was the most used PROM in the studies included in this review. It consists of ten written self-reporting items evaluating the quality of life of patients with OM, as the capacity of talking and sleeping (Stiff et al., 2006). OMDQ MTS has no validation to the pediatric population, owing its structure of a written questionnaire. In 2011, Tomlinson et al. developed a modified OMDQ for use in children, adding faces as answers to the questions, similar to what they did elaborating the ChiMES, trying to make it easier for children to understand and changing from self-report to parent-report. These modifications were considered reliable for the assessment of symptoms and functionality in relation to children's OM **(**Tomlinson et al., 2011; Manji et al., 2012; Wong et al., 2023 Meryk et al 2022) investigating the use of PROM to identify adverse effects in pediatric patients with cancer and provide individualized supportive care using found that PROM score was associated with adverse effects and OM was among the 5 most common. Focusing on the highest symptom burden, strong pain was reported in cases of OM. More importantly, 1 day before the clinical manifestation, pain was reported with the highest symptom burden for OM.

Some limitations may be considered in this study such as the low reporting of pain scales and PROMs which impacted in our analysis of these results and the real importance of using these assessments on the pediatric population.

Our study, in addition to systematically compiling the methods of OM assessment in pediatric oncology patients, also aimed to provide guidance for enhancing the evaluation of these patients in clinical practice and future studies. Therefore, we propose that ChiMES should be used to evaluate and assess OM in children due to its construction considering children, its subjective form to answer the majority of questions – using face expressions –, evaluating pain and being a form of gathering patients' related outcomes. Also, clinical evaluation of oral mucosa using WHO should be done whenever possible as it allows for clinical analysis by specialized professionals. Furthermore, utilizing a PROM is necessary in the management of pediatric oncology patients to provide more comprehensive healthcare.

Conclusion

The accurate assessment of OM in pediatric oncological patients is crucial for effective management, impacting treatment outcomes and hospitalization. However, existing scales fail to adequately assess OM in this group of patients. While the WHO scale is commonly used

despite its adult-focused design, it lacks sufficient detail for pediatric OM assessment, relying on child cooperation for comprehensive oral cavity examination. In contrast, the CHIMES scale offers a child-friendly approach, enabling self-reporting and better understanding of the patient's condition and pain. Though lacking specific lesion assessment, combining CHIMES with the WHO scale can provide a comprehensive evaluation, integrating functional and anatomical information alongside the child's perspective. Additionally, supplementing with pain scales and PROMs enhances assessment accuracy, optimizing patients' evaluation and quality of life in oncological care.

Conflicts of interest/Competing interests

The authors declare no competing interests.

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References

World Health Organisation. International Agency for Research on Cancer. Global Cancer Observatory. Available in https://gco.iarc.fr/tomorrow/en/dataviz/isotype?age_end=0&single_unit=10000&years=2040&types=0. Accessed on May 30, 2023.

Atun, R., Bhakta, N., Denburg, A., Frazier, A. L., Friedrich, P., Gupta, S., Lam, C. G., Ward, Z. J., Yeh, J. M., Allemani, C., Coleman, M. P., Di Carlo, V., Loucaides, E., Fitchett, E., Girardi, F., Horton, S. E., Bray, F., Steliarova-Foucher, E., Sullivan, R., Aitken, J. F., … Rodriguez-Galindo, C. (2020). Sustainable care for children with cancer: a Lancet Oncology Commission. *The Lancet. Oncology*, *21*(4), e185–e224. https://doi.org/10.1016/S1470-2045(20)30022-X

Ward, Z. J., Yeh, J. M., Bhakta, N., Frazier, A. L., Girardi, F., & Atun, R. (2019). Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *The Lancet. Oncology*, *20*(7), 972–983. https://doi.org/10.1016/S1470-2045(19)30273-6

Erdmann, F., Frederiksen, L. E., Bonaventure, A., Mader, L., Hasle, H., Robison, L. L., & Winther, J. F. (2021). Childhood cancer: Survival, treatment modalities, late effects and improvements over time. *Cancer epidemiology*, *71*(Pt B), 101733. https://doi.org/10.1016/j.canep.2020.101733

Kwon Y. (2016). Mechanism-based management for mucositis: option for treating side effects without compromising the efficacy of cancer therapy. OncoTargets and therapy, 9, 2007–2016. https://doi.org/10.2147/OTT.S96899

Silva, I. M. V., Donaduzzi, L. C., Perini, C. C., Couto, S. A. B., Werneck, R. I., de Araújo, M. R., Kurahashi, M., Johann, A. C. B. R., Azevedo-Alanis, L. R., Vieira, A. R., & Couto-Souza, P. H. (2021). Association of xerostomia and taste alterations of patients receiving antineoplastic chemotherapy: A cause for nutritional concern. Clinical nutrition ESPEN, 43, 532–535. https://doi.org/10.1016/j.clnesp.2021.03.006

Strojan, P., Hutcheson, K. A., Eisbruch, A., Beitler, J. J., Langendijk, J. A., Lee, A. W. M., Corry, J., Mendenhall, W. M., Smee, R., Rinaldo, A., & Ferlito, A. (2017). Treatment of late sequelae after radiotherapy for head and neck cancer. Cancer treatment reviews, 59, 79–92. https://doi.org/10.1016/j.ctrv.2017.07.003

Correa, M. E. P., Cheng, K. K. F., Chiang, K., Kandwal, A., Loprinzi, C. L., Mori, T., Potting, C., Rouleau, T., Toro, J. J., Ranna, V., Vaddi, A., Peterson, D. E., Bossi, P., Lalla, R. V., & Elad, S. (2020). Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 28(5), 2449–2456. https://doi.org/10.1007/s00520-019-05217-x

Sonis S. T. (2021). Treatment for Oral Mucositis-Current Options and an Update of Small Molecules Under Development. Current treatment options in oncology, 22(3), 25. https://doi.org/10.1007/s11864-021-00823-6

Vasconcelos, R. M., Sanfilippo, N., Paster, B. J., Kerr, A. R., Li, Y., Ramalho, L., Queiroz, E. L., Smith, B., Sonis, S. T., & Corby, P. M. (2016). Host-Microbiome Cross-talk in Oral Mucositis. Journal of dental research, 95(7), 725–733. https://doi.org/10.1177/0022034516641890

Elad, S., Yarom, N., Zadik, Y., Kuten-Shorrer, M., & Sonis, S. T. (2022). The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies. *CA: a cancer journal for clinicians*, *72*(1), 57–77. https://doi.org/10.3322/caac.21704

Villa, A., & Sonis, S. T. (2020). An update on pharmacotherapies in active development for the management of cancer regimen-associated oral mucositis. Expert opinion on pharmacotherapy, 21(5), 541–548. https://doi.org/10.1080/14656566.2020.1718652

Sung, L., Robinson, P., Treister, N., Baggott, T., Gibson, P., Tissing, W., Wiernikowski, J., Brinklow, J., & Dupuis, L. L. (2017). Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell

transplantation. BMJ supportive & palliative care, 7(1), 7–16. https://doi.org/10.1136/bmjspcare-2014-000804

Sonis S. T. (2013). Oral mucositis in head and neck cancer: risk, biology, and management. American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting, 10.1200/EdBook_AM.2013.33.e236. https://doi.org/10.14694/EdBook_AM.2013.33.e236

Bockel, S., Vallard, A., Lévy, A., François, S., Bourdis, M., Le Gallic, C., Riccobono, D., Annede, P., Drouet, M., Tao, Y., Blanchard, P., Deutsch, É., Magné, N., & Chargari, C. (2018). Pharmacological modulation of radiation-induced oral mucosal complications. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique, 22(5), 429–437. https://doi.org/10.1016/j.canrad.2017.11.006

Chen, C., Zhang, Q., Yu, W., Chang, B., & Le, A. D. (2020). Oral Mucositis: An Update on Innate Immunity and New Interventional Targets. *Journal of dental research*, *99*(10), 1122–1130. https://doi.org/10.1177/0022034520925421

Elad, S., Cheng, K. K. F., Lalla, R. V., Yarom, N., Hong, C., Logan, R. M., Bowen, J., Gibson, R., Saunders, D. P., Zadik, Y., Ariyawardana, A., Correa, M. E., Ranna, V., Bossi, P., & Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) (2020). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer, 126(19), 4423–4431. https://doi.org/10.1002/cncr.33100

Sonis, S. T., Hashemi, S., Epstein, J. B., Nair, R. G., & Raber-Durlacher, J. E. (2016). Could the biological robustness of low level laser therapy (Photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. Oral oncology, 54, 7–14. https://doi.org/10.1016/j.oraloncology.2016.01.005

Zecha, J. A., Raber-Durlacher, J. E., Nair, R. G., Epstein, J. B., Sonis, S. T., Elad, S., Hamblin, M. R., Barasch, A., Migliorati, C. A., Milstein, D. M., Genot, M. T., Lansaat, L., van der Brink, R., Arnabat-Dominguez, J., van der Molen, L., Jacobi, I., van Diessen, J., de Lange, J., Smeele, L. E., Schubert, M. M., … Bensadoun, R. J. (2016). Low level laser

therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 24(6), 2781–2792. https://doi.org/10.1007/s00520-016-3152-z

Redman MG, Harris K, Phillips BS*Low-level laser therapy for oral mucositis in children with cancer*Archives of Disease in Childhood 2022;107:128-133.

Correa, M. E. P., Cheng, K. K. F., Chiang, K., Kandwal, A., Loprinzi, C. L., Mori, T., Potting, C., Rouleau, T., Toro, J. J., Ranna, V., Vaddi, A., Peterson, D. E., Bossi, P., Lalla, R. V., & Elad, S. (2020). Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 28(5), 2449–2456. https://doi.org/10.1007/s00520-019-05217-x

Lai, C. C., Chen, S. Y., Tu, Y. K., Ding, Y. W., & Lin, J. J. (2021). Effectiveness of low level laser therapy versus cryotherapy in cancer patients with oral mucositis: Systematic review and network meta-analysis. Critical reviews in oncology/hematology, 160, 103276. https://doi.org/10.1016/j.critrevonc.2021.103276

Tomlinson, D., Judd, P., Hendershot, E., Maloney, A. M., & Sung, L. (2008). Establishing literature-based items for an oral mucositis assessment tool in children. Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses, 25(3), 139–147. https://doi.org/10.1177/1043454208317235

Eilers, J., & Epstein, J. B. (2004). Assessment and measurement of oral mucositis. Seminars in oncology nursing, 20(1), 22–29. https://doi.org/10.1053/j.soncn.2003.10.005

Jacobs, S., Baggott, C., Agarwal, R., Hesser, T., Schechter, T., Judd, P., Tomlinson, D., Beyene, J., & Sung, L. (2013). Validation of the Children's International Mucositis Evaluation Scale (ChIMES) in paediatric cancer and SCT. British journal of cancer, 109(10), 2515–2522. https://doi.org/10.1038/bjc.2013.618

Cheng, K. K., Molassiotis, A., Chang, A. M., Wai, W. C., & Cheung, S. S. (2001). Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. European journal of cancer (Oxford, England : 1990), 37(16), 2056–2063. https://doi.org/10.1016/s0959-8049(01)00098-3

Tomlinson, D., Judd, P., Hendershot, E., Maloney, A. M., & Sung, L. (2007). Measurement of oral mucositis in children: a review of the literature. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 15(11), 1251–1258. https://doi.org/10.1007/s00520-007-0323-y

Gibson, F., Cargill, J., Allison, J., Begent, J., Cole, S., Stone, J., & Lucas, V. (2006). Establishing content validity of the oral assessment guide in children and young people. European journal of cancer (Oxford, England : 1990), 42(12), 1817–1825. https://doi.org/10.1016/j.ejca.2006.02.018

Cheng, K. K., Leung, S. F., Thompson, D. R., Tai, J. W., Liang, R. H., Kan, A. S., Ying, F. W., & Yeung, R. M. (2007). New measure of health-related quality of life for patients with oropharyngeal mucositis: development and preliminary psychometric evaluation. Cancer, 109(12), 2590–2599. https://doi.org/10.1002/cncr.22730

Sonis, S. T., Eilers, J. P., Epstein, J. B., LeVeque, F. G., Liggett, W. H., Jr, Mulagha, M. T., Peterson, D. E., Rose, A. H., Schubert, M. M., Spijkervet, F. K., & Wittes, J. P. (1999). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. Cancer, 85(10), 2103–2113. https://doi.org/10.1002/(sici)1097-0142(19990515)85:10<2103::aid-cncr2>3.0.co;2-0

McGuire, D. B., Peterson, D. E., Muller, S., Owen, D. C., Slemmons, M. F., & Schubert, M. M. (2002). The 20 item oral mucositis index: reliability and validity in bone marrow and stem cell transplant patients. Cancer investigation, 20(7-8), 893–903. https://doi.org/10.1081/cnv-120005902

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J.

M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed.), 372, n71. https://doi.org/10.1136/bmj.n71

Moola S, Munn Z, Tufanaru C et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from https://synthesismanual.jbi.global

Eilers, June and Berger, Ann, "Oral Assessment Guide" (1988). Guides and Handouts: College of Nursing.

Aoki, T., Kudo, M., Endo, M., Nakayama, Y., Amano, A., Naito, M., & Ota, Y. (2019). Inter-rater reliability of the Oral Assessment Guide for oral cancer patients between nurses and dental hygienists: the difficulties in objectively assessing oral health. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 27(5), 1673–1677. https://doi.org/10.1007/s00520-018-4412-x

World Health Organization. Handbook for reporting results of cancer treatment. Geneva, Switzerland: World Health Organization, 1979.

U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. 2017.

Tomlinson, D., Gibson, F., Treister, N., Baggott, C., Judd, P., Hendershot, E., Maloney, A. M., Doyle, J., Feldman, B., & Sung, L. (2009). Designing an oral mucositis assessment instrument for use in children: generating items using a nominal group technique. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 17(5), 555–562. https://doi.org/10.1007/s00520-008-0523-0

Hong, C. H. L., Gueiros, L. A., Fulton, J. S., Cheng, K. K. F., Kandwal, A., Galiti, D., Fall-Dickson, J. M., Johansen, J., Ameringer, S., Kataoka, T., Weikel, D., Eilers, J., Ranna, V., Vaddi, A., Lalla, R. V., Bossi, P., Elad, S., & Mucositis Study Group of the Multinational

Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) (2019). Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 27(10), 3949–3967. https://doi.org/10.1007/s00520-019-04848-4

Cheng, K. K., Lee, J., Leung, S. F., Liang, R. H., Tai, J. W., Yeung, R. M., & Thompson, D. R. (2011). Use of Rasch analysis in the evaluation of the Oropharyngeal Mucositis Quality Of Life Scale. Nursing research, 60(4), 256–263. https://doi.org/10.1097/NNR.0b013e318221f731

Huskisson E. C. (1974). Measurement of pain. Lancet (London, England), 2(7889), 1127–1131. https://doi.org/10.1016/s0140-6736(74)90884-8

Garra, G., Singer, A. J., Taira, B. R., Chohan, J., Cardoz, H., Chisena, E., & Thode, H. C., Jr (2010). Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine, 17(1), 50–54. https://doi.org/10.1111/j.1553-2712.2009.00620.x

Haefeli, M., & Elfering, A. (2006). Pain assessment. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society, 15 Suppl 1(Suppl 1), S17–S24. https://doi.org/10.1007/s00586-005-1044-x

Hicks, C. L., von Baeyer, C. L., Spafford, P. A., van Korlaar, I., & Goodenough, B. (2001). The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain, 93(2), 173–183. https://doi.org/10.1016/S0304-3959(01)00314-1

Marec-Berard, P., Gomez, F., Combet, S., Thibault, P., Moine, P. L., & Bergeron, C. (2015). HEDEN Pain Scale: A Shortened Behavioral Scale for Assessment of Prolonged Cancer or Postsurgical Pain in Children Aged 2 to 6 Years. Pediatric hematology and oncology, 32(5), 291–303. https://doi.org/10.3109/08880018.2015.1005324

Crellin, D. J., Harrison, D., Santamaria, N., & Babl, F. E. (2015). Systematic review of the Face, Legs, Activity, Cry and Consolability scale for assessing pain in infants and children: is it reliable, valid, and feasible for use?. Pain, 156(11), 2132–2151. https://doi.org/10.1097/j.pain.0000000000000305

Merkel, S. I., Voepel-Lewis, T., Shayevitz, J. R., & Malviya, S. (1997). The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatric nursing, 23(3), 293–297.

Mazhari, F., Shirazi, A. S., & Shabzendehdar, M. (2019). Management of oral mucositis in pediatric patients receiving cancer therapy: A systematic review and meta-analysis. Pediatric blood & cancer, 66(3), e27403. https://doi.org/10.1002/pbc.27403

Hong, C. H. L., Gueiros, L. A., Fulton, J. S., Cheng, K. K. F., Kandwal, A., Galiti, D., Fall-Dickson, J. M., Johansen, J., Ameringer, S., Kataoka, T., Weikel, D., Eilers, J., Ranna, V., Vaddi, A., Lalla, R. V., Bossi, P., Elad, S., & Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) (2019). Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 27(10), 3949–3967. https://doi.org/10.1007/s00520-019-04848-4

Kamsvåg-Magnusson, T., Thorsell-Cederberg, J., Svanberg, A., von Essen, L., Arvidson, J., Mellgren, K., Toporski, J., & Ljungman, G. (2014). Parents and children's perceptions of distress related to oral mucositis during haematopoietic stem cell transplantation. Acta paediatrica (Oslo, Norway : 1992), 103(6), 630–636. https://doi.org/10.1111/apa.12627

Figliolia, S. L., Oliveira, D. T., Pereira, M. C., Lauris, J. R., Maurício, A. R., Oliveira, D. T., & Mello de Andrea, M. L. (2008). Oral mucositis in acute lymphoblastic leukaemia: analysis of 169 paediatric patients. Oral diseases, 14(8), 761–766. https://doi.org/10.1111/j.1601-0825.2008.01468.x

Bedoui, Y., Guillot, X., Sélambarom, J., Guiraud, P., Giry, C., Jaffar-Bandjee, M. C., Ralandison, S., & Gasque, P. (2019). Methotrexate an Old Drug with New Tricks.

International journal of molecular sciences, 20(20), 5023. https://doi.org/10.3390/ijms20205023

Campbell, J. M., Bateman, E., Stephenson, M. D., Bowen, J. M., Keefe, D. M., & Peters, M. D. (2016). Methotrexate-induced toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. Cancer chemotherapy and pharmacology, 78(1), 27–39. https://doi.org/10.1007/s00280-016-3043-5

Van der Beek, J. N., Oosterom, N., Pieters, R., de Jonge, R., van den Heuvel-Eibrink, M. M., & Heil, S. G. (2019). The effect of leucovorin rescue therapy on methotrexate-induced oral mucositis in the treatment of paediatric ALL: A systematic review. Critical reviews in oncology/hematology, 142, 1–8. https://doi.org/10.1016/j.critrevonc.2019.07.003

Cheng K. K. (2008). Association of plasma methotrexate, neutropenia, hepatic dysfunction, nausea/vomiting and oral mucositis in children with cancer. European journal of cancer care, 17(3), 306–311. https://doi.org/10.1111/j.1365-2354.2007.00843.x

Ku, M., Bazargan, A., & Tam, C. (2020). Addition of low dose acetazolamide as an adjunct in patients undergoing high dose methotrexate is safe and beneficial. Internal medicine journal, 50(3), 357–362. https://doi.org/10.1111/imj.14468

Valer, J. B., Curra, M., Gabriel, A. F., Schmidt, T. R., Ferreira, M. B. C., Roesler, R., Evangelista, J. M. C., Martins, M. A. T., Gregianin, L., & Martins, M. D. (2021). International journal of paediatric dentistry, 31(2), 238–246. https://doi.org/10.1111/ipd.12718

Zadik, Y., Arany, P. R., Fregnani, E. R., Bossi, P., Antunes, H. S., Bensadoun, R. J., Gueiros, L. A., Majorana, A., Nair, R. G., Ranna, V., Tissing, W. J. E., Vaddi, A., Lubart, R., Migliorati, C. A., Lalla, R. V., Cheng, K. K. F., Elad, S., & Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) (2019). Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 27(10), 3969–3983. https://doi.org/10.1007/s00520-019-04890-2

Brown, C. G., & Wingard, J. (2004). Clinical consequences of oral mucositis. Seminars in oncology nursing, 20(1), 16–21. https://doi.org/10.1053/j.soncn.2003.10.004

Attinà, G., Romano, A., Maurizi, P., D'Amuri, S., Mastrangelo, S., Capozza, M. A., Triarico, S., & Ruggiero, A. (2021). Management of Oral Mucositis in Children With Malignant Solid Tumors. Frontiers in oncology, 11, 599243. https://doi.org/10.3389/fonc.2021.599243

Tomlinson, D., Gibson, F., Treister, N., Baggott, C., Judd, P., Hendershot, E., Maloney, A. M., Doyle, J., Feldman, B., Kwong, K., & Sung, L. (2010). Refinement of the Children's International Mucositis Evaluation Scale (ChIMES): child and parent perspectives on understandability, content validity and acceptability. European journal of oncology nursing : the official journal of European Oncology Nursing Society, 14(1), 29–41. https://doi.org/10.1016/j.ejon.2009.10.004

Paiva, B. S. R., Barroso, E. M., Cadamuro, S. A., Paula, L. A. B., Pirola, W. E., Serrano, C. V. M. P., & Paiva, C. E. (2018). The Children's International Mucositis Evaluation Scale Is Valid and Reliable for the Assessment of Mucositis Among Brazilian Children With Cancer. Journal of pain and symptom management, 56(5), 774–780.e2. https://doi.org/10.1016/j.jpainsymman.2018.07.015

McGrath, P. J., Walco, G. A., Turk, D. C., Dworkin, R. H., Brown, M. T., Davidson, K., Eccleston, C., Finley, G. A., Goldschneider, K., Haverkos, L., Hertz, S. H., Ljungman, G., Palermo, T., Rappaport, B. A., Rhodes, T., Schechter, N., Scott, J., Sethna, N., Svensson, O. K., Stinson, J., … PedIMMPACT (2008). Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. The journal of pain, 9(9), 771–783. https://doi.org/10.1016/j.jpain.2008.04.007

Pereira N. F., Silva P. V. R., Fukuoka C. Y., Michel-Crosato E., Goncalves A. S., Alves F. A., Vieira G. M. M., Biazevic M. G. H. (2018) Measurement of oral health quality of life among patients who underwent haematopoietic stem-cell transplantation. Braz. Oral Res., 32(78), 1-7 https://doi.org/10.1590/1807-3107BOR-2018.vol32.0078

Churruca, K., Pomare, C., Ellis, L. A., Long, J. C., Henderson, S. B., Murphy, L. E. D., Leahy, C. J., & Braithwaite, J. (2021). Patient-reported outcome measures (PROMs): A

review of generic and condition-specific measures and a discussion of trends and issues. Health expectations : an international journal of public participation in health care and health policy, 24(4), 1015–1024. https://doi.org/10.1111/hex.13254

McGee R. G. (2020). How to Include Patient-Reported Outcome Measures in Clinical Trials. Current osteoporosis reports, 18(5), 480–485. https://doi.org/10.1007/s11914-020-00611-5

Meryk, A., Kropshofer, G., Hetzer, B., Riedl, D., Lehmann, J., Rumpold, G., Haid, A., Schneeberger-Carta, V., Holzner, B., & Crazzolara, R. (2022). Use of Daily Patient-Reported Outcome Measurements in Pediatric Cancer Care. JAMA network open, 5(7), e2223701. https://doi.org/10.1001/jamanetworkopen.2022.23701

Martins, A. F. L., Morais, M. O., de Sousa-Neto, S. S., de Jesus, A. P. G., Nogueira, T. E., Valadares, M. C., Freitas, N. M. A., Batista, A. C., Leles, C. R., & Mendonça, E. F. (2021). Photobiomodulation reduces the impact of radiotherapy on oral health-related quality of life due to mucositis-related symptoms in head and neck cancer patients. Lasers in medical science, 36(4), 903–912. https://doi.org/10.1007/s10103-020-03167-z

Lopes Martins, A. F., Nogueira, T. E., Morais, M. O., de Sousa-Neto, S. S., Oton-Leite, A. F., Valadares, M. C., Aires Freitas, N. M., Leles, C. R., & Mendonça, E. F. (2021). Cost-effectiveness randomized clinical trial on the effect of photobiomodulation therapy for prevention of radiotherapy-induced severe oral mucositis in a Brazilian cancer hospital setting. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 29(3), 1245–1256. https://doi.org/10.1007/s00520-020-05607-6

Stiff, P. J., Erder, H., Bensinger, W. I., Emmanouilides, C., Gentile, T., Isitt, J., Lu, Z. J., & Spielberger, R. (2006). Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). Bone marrow transplantation, 37(4), 393–401. https://doi.org/10.1038/sj.bmt.1705250

Cheng, K. K., Lee, V., Li, C. H., Goggins, W., Thompson, D. R., Yuen, H. L., & Epstein, J. B. (2011). Incidence and risk factors of oral mucositis in paediatric and adolescent patients

undergoing chemotherapy. Oral oncology, 47(3), 153–162. https://doi.org/10.1016/j.oraloncology.2010.11.019

Tomlinson, D., Ethier, M. C., Judd, P., Doyle, J., Gassas, A., Naqvi, A., & Sung, L. (2011). Reliability and construct validity of the oral mucositis daily questionnaire in children with cancer. European journal of cancer (Oxford, England : 1990), 47(3), 383–388. https://doi.org/10.1016/j.ejca.2010.09.018

Wong, S. P., Tan, S. M., Danaee, M., Muhamad, K., Jamal, M., Islahudin, F., Khairudin, F., Edmund, S. C., Chang, K. M., Zakaria, M. Z., Lim, Y. A. L., & Rajasuriar, R. (2022). Psychometric evaluation of Oral Mucositis Daily Questionnaire: A cross-cultural adaptation of the Malay version in multiethnic adult autologous stem cell transplant. Asia-Pacific journal of oncology nursing, 10(2), 100180. https://doi.org/10.1016/j.apjon.2022.100180

Sung, L., Tomlinson, G. A., Greenberg, M. L., Koren, G., Judd, P., Ota, S., & Feldman, B. M. (2007). Validation of the oral mucositis assessment scale in pediatric cancer. Pediatric blood & cancer, 49(2), 149–153. https://doi.org/10.1002/pbc.20863
Huskisson E. C. (1974). Measurement of pain. Lancet (London, England), 2(7889), 1127–1131. https://doi.org/10.1016/s0140-6736(74)90884-8

Chiarotto A, Maxwell LJ, Ostelo RW, Boers M, Tugwell P, Terwee CB. Measurement Properties of Visual Analogue Scale, Numeric Rating Scale, and Pain Severity Subscale of the Brief Pain Inventory in Patients With Low Back Pain: A Systematic Review. J Pain. 2019 Mar;20(3):245-263. doi: 10.1016/j.jpain.2018.07.009. Epub 2018 Aug 10. PMID: 30099210.

Tomlinson, D., von Baeyer, C. L., Stinson, J. N., & Sung, L. (2010). A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics, 126(5), e1168–e1198. https://doi.org/10.1542/peds.2010-1609

Appendix 1. Search strategy of the systematic review.

Database	Search Strategy
MEDLINE/PubMed	(((Stomatitis OR Stomatitides OR "Oral Mucositis" OR "Mucositides, Oral" OR "Oral Mucositides" OR Oromucositis OR Oromucositides OR "Mucositis, Oral")) AND ((Child OR Children OR Pediatric OR Pediatrics OR Paediatric OR Infant))) AND (("Patient Reported Outcome Measures" OR "Patient Reported Outcome Measure" OR "Patient Reported Outcomes" OR "Outcome, Patient Reported" OR "Patient Reported Outcome" OR "Patient-Reported Outcome" OR "Outcome, Patient-Reported" OR "Patient-Reported Outcomes" OR Assessment OR "Oral Mucositis Assessment Scale" OR "Instrument Development" OR "Measurement of Oral Mucositis" OR "Evaluation Scales of Oral Mucositis"))
EMBASE	('stomatitis'/exp OR stomatitis OR stomatitides OR 'oral mucositis'/exp OR 'oral mucositis' OR 'mucositides, oral' OR 'oral mucositides'/exp OR 'oral mucositides' OR 'oromucositis'/exp OR oromucositis OR 'oromucositides'/exp OR oromucositides OR 'mucositis, oral') AND ('child'/exp OR child OR 'children'/exp OR children OR 'pediatric'/exp OR pediatric OR 'pediatrics'/exp OR pediatrics OR 'paediatric'/exp OR paediatric OR 'infant'/exp OR infant) AND ('patient reported outcome measures'/exp OR 'patient reported outcome measures' OR 'patient reported outcome measure'/exp OR 'patient reported outcome measure' OR 'patient reported outcomes'/exp OR 'patient reported outcomes' OR 'outcome, patient reported' OR 'patient reported outcome'/exp OR 'patient reported outcome' OR 'patient-reported outcome'/exp OR 'patient-reported outcome' OR 'outcome, patient-reported' OR 'patient-reported outcomes' OR 'assessment'/exp OR assessment OR 'oral mucositis assessment scale'/exp OR 'oral mucositis assessment scale' OR 'instrument development'/exp OR 'instrument development' OR 'measurement of oral mucositis' OR 'evaluation scales of oral mucositis')
Web of Science	((ALL=((Stomatitis OR Stomatitides OR “Oral Mucositis” OR “Mucositides, Oral” OR “Oral Mucositides” OR Oromucositis OR Oromucositides OR “Mucositis, Oral”))) AND ALL=((Child OR Children OR Pediatric OR Pediatrics OR Paediatric OR Infant))) AND ALL=((“Patient Reported Outcome

	Measures” OR “Patient Reported Outcome Measure” OR “Patient Reported Outcomes” OR “Outcome, Patient Reported” OR “Patient Reported Outcome” OR “Patient-Reported Outcome” OR “Outcome, Patient-Reported” OR “Patient-Reported Outcomes” OR Assessment OR “Oral Mucositis Assessment Scale” OR “Instrument Development” OR “Measurement of Oral Mucositis” OR "Evaluation Scales of Oral Mucositis”))
Scopus	TITLE-ABS-KEY (stomatitis OR stomatitides OR "Oral Mucositis" OR "Mucositides, Oral" OR "Oral Mucositides" OR oromucositis OR oromucositides OR "Mucositis, Oral") AND TITLE-ABS-KEY (child OR children OR pediatric OR pediatrics OR paediatric OR infant) AND TITLE-ABS-KEY ("Patient Reported Outcome Measures" OR "Patient Reported Outcome Measure" OR "Patient Reported Outcomes" OR "Outcome, Patient Reported" OR "Patient Reported Outcome" OR "Patient-Reported Outcome" OR "Outcome, Patient-Reported" OR "Patient-Reported Outcomes" OR assessment OR "Oral Mucositis Assessment Scale" OR "Instrument Development" OR "Measurement of Oral Mucositis" OR "Evaluation Scales of Oral Mucositis")
Pro Quest	TI,AB(Stomatitis OR Stomatitides OR “Oral Mucositis” OR “Mucositides, Oral” OR “Oral Mucositides” OR Oromucositis OR Oromucositides OR “Mucositis, Oral”) AND TI,AB(Child OR Children OR Pediatric OR Pediatrics OR Paediatric OR Infant) AND TI,AB(“Patient Reported Outcome Measures” OR “Patient Reported Outcome Measure” OR “Patient Reported Outcomes” OR “Outcome, Patient Reported” OR “Patient Reported Outcome” OR “Patient-Reported Outcome” OR “Outcome, Patient-Reported” OR “Patient-Reported Outcomes” OR Assessment OR “Oral Mucositis Assessment Scale” OR “Instrument Development” OR “Measurement of Oral Mucositis” OR “Evaluation Scales of Oral Mucositis”)
Google Scholar	(“Oral Mucositis”) AND (Children OR Pediatric) AND (“Patient Reported Outcome Measures”)

Appendix 2. Articles with exclusion reasons.

Author	Year	Reason for exclusion*
Izutsu, K. T.	1981	3
Berkowitz, R. J.	1983	1
Raether, D.	1989	3
Mackie, A. M.	1991	6
Donaldson, G. W.	1992	6
McGuire, D. B.	1993	1
Elad, S.	1999	3
Rapoport, A. P.	1999	3
Oberbaum, M.	2001	3
Whelan, H. T.	2002	3
Cella, D.	2003	3
Costa, E. M.	2003	6
Haytac, M. C.	2004	1
Gordón-Núñez, M. A.	2005	1
Mess, E.	2005	1
Gori, E.	2007	3

Abramoff, M. M.	2008	3
Cai, Q.	2008	3
Figliolia, S. L.	2008	6
Maiguma, T.	2008	1
Taheri, M.	2008	3
Jebabli, N.	2009	1
Tomazevic, T.	2009	1
Ward, E.	2009	3
Hodgson, B.	2010	3
Csordás, K.	2011	2
Márton, I.	2011	1
Yilmaz, M.	2011	1
Lalioui, S.	2012	1
Pels, E.	2012	6
Revel-Vilk, S.	2012	1
Steinmann, D.	2012	4
Cauwels, R.	2013	5
Elad, S.	2013	3

Khurana, H.	2013	1
Ottaviani, G.	2013	1
Thomaz, E. B. A. F.	2013	6
Kaewmanee, J.	2014	1
Barkokebas, A.	2015	3
Colita, A.	2015	5
Dragomir, M. D.	2015	1
Gautam, A. P.	2015	3
Patiroglu, T.	2015	5
Pels, E.	2015	6
Righini-Grunder, F.	2015	6
Silva, L. C.	2015	3
Bezinelli, L. M.	2016	3
Boris, S. P.	2016	2
Mansouri, P.	2016	3
Treister, N. S.	2016	3
Bhatt, N.	2017	3
Kramer, K.	2017	5

Salvador, D. R. N.	2017	3
Treister, N	2017	3
Graul-Conroy, A.	2018	3
Krupski, M. C.	2018	5
Yadlapalli, D. C.	2018	5
Al-Qalamji, M. A. N.	2019	3
Myat, S.	2019	1
Pai, R. R.	2019	5
Adams, L. K.	2020	3
de Paula Eduardo, F.	2020	3
Elsabagh, H. H.	2020	3
Purba, H. F.	2020	3
Tomlinson	2020	1
Alsheyyab, F.	2021	6
Ebert, N.	2021	3
Garaventa, A.	2021	3
Garming Legert, K.	2021	3
Guberti, M.	2021	3

Kamallan, S. R.	2021	2
Malek, F.	2021	1
Wang, Y.	2021	6
Hurrell, L.	2022	1
Karaman, K.	2022	1
Katzenstein, H. M.	2022	3
Morgenstern, D.	2022	1
Nakabiri, J.	2022	1
Parkhideh, S.	2022	3
Withycombe, Janice S.	2022	6
Alfeky, F. M.	2023	3
Falahinia, N.	2023	6
Thornton, C. P.	2023	1

*1- Papers without access; 2-Another language; 3- Not (just) children; 4- Outline; 5-Letter/Conference abstract; 6-No information (does not mention any scale).

Appendix 3. Studies were included in the review.

Lever, S. A., Dupuis, L. L., & Chan, H. S. (1987). Comparative evaluation of benzydamine oral rinse in children with antineoplastic-induced stomatitis. *Drug intelligence & clinical pharmacy*, *21*(4), 359–361. https://doi.org/10.1177/106002808702100412

Levy-Polack, M. P., Sebelli, P., & Polack, N. L. (1998). Incidence of oral complications and application of a preventive protocol in children with acute leukemia. *Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*, *18*(5), 189–193. https://doi.org/10.1111/j.1754-4505.1998.tb01738.x

Estlin, E. J., Pinkerton, C. R., Lewis, I. J., Lashford, L., McDowell, H., Morland, B., Kohler, J., Newell, D. R., Boddy, A. V., Taylor, G. A., Price, L., Ablett, S., Hobson, R., Pitsiladis, M., Brampton, M., Clendeninn, N., Johnston, A., & Pearson, A. D. (2001). A phase I study of nolatrexed dihydrochloride in children with advanced cancer. A United Kingdom Children's Cancer Study Group Investigation. *British journal of cancer*, *84*(1), 11–18. https://doi.org/10.1054/bjoc.2000.1569

Cheng, K. K., Molassiotis, A., & Chang, A. M. (2002). An oral care protocol intervention to prevent chemotherapy-induced oral mucositis in paediatric cancer patients: a pilot study. *European journal of oncology nursing : the official journal of European Oncology Nursing Society*, *6*(2), 66–73. https://doi.org/10.1054/ejon.2001.0161

Cheng, K. K., & Chang, A. M. (2003). Palliation of oral mucositis symptoms in pediatric patients treated with cancer chemotherapy. *Cancer nursing*, *26*(6), 476–484. https://doi.org/10.1097/00002820-200312000-00007

Chen, C. F., Wang, R. H., Cheng, S. N., & Chang, Y. C. (2004). Assessment of chemotherapy-induced oral complications in children with cancer. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses*, *21*(1), 33–39. https://doi.org/10.1177/1043454203259947

Cheng, K. K., Chang, A. M., & Yuen, M. P. (2004). Prevention of oral mucositis in paediatric patients treated with chemotherapy; a randomised crossover trial comparing two protocols of oral care. *European journal of cancer (Oxford, England : 1990)*, *40*(8), 1208–1216. https://doi.org/10.1016/j.ejca.2003.10.023

Schmid, I., Schmitt, M., Streiter, M., Meilbeck, R., Albert, M. H., Reinhardt, D., & Stachel, D. (2006). Parenteral nutrition is not superior to replacement fluid therapy for the supportive

treatment of chemotherapy induced oral mucositis in children. *European journal of cancer (Oxford, England : 1990)*, *42*(2), 205–211. https://doi.org/10.1016/j.ejca.2005.09.020

Bechard, L. J., Guinan, E. C., Feldman, H. A., Tang, V., & Duggan, C. (2007). Prognostic factors in the resumption of oral dietary intake after allogeneic hematopoietic stem cell transplantation (HSCT) in children. *JPEN. Journal of parenteral and enteral nutrition*, *31*(4), 295–301. https://doi.org/10.1177/0148607107031004295

Cruz, L. B., Ribeiro, A. S., Rech, A., Rosa, L. G., Castro, C. G., Jr, & Brunetto, A. L. (2007). Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. *Pediatric blood & cancer*, *48*(4), 435–440. https://doi.org/10.1002/pbc.20943

Cubukcu, C. E., & Sevinir, B. (2007). Debridement could be a solution to promote healing of established oral mucositis in children. *European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry*, *8*(2), 105–112. https://doi.org/10.1007/BF03262578

de Koning, B. A., Philipsen-Geerling, B., Hoijer, M., Hählen, K., Büller, H. A., & Pieters, R. (2007). Protection against chemotherapy induced mucositis by TGF-beta(2) in childhood cancer patients: results from a randomized cross-over study. *Pediatric blood & cancer*, *48*(5), 532–539. https://doi.org/10.1002/pbc.20910

El-Housseiny, A. A., Saleh, S. M., El-Masry, A. A., & Allam, A. A. (2007). Assessment of oral complications in children receiving chemotherapy. *The Journal of clinical pediatric dentistry*, *31*(4), 267–273. https://doi.org/10.17796/jcpd.31.4.cq752m6173142r28

El-Housseiny, A. A., Saleh, S. M., El-Masry, A. A., & Allam, A. A. (2007). The effectiveness of vitamin "E" in the treatment of oral mucositis in children receiving chemotherapy. *The Journal of clinical pediatric dentistry*, *31*(3), 167–170.

Gandemer, V., Le Deley, M. C., Dollfus, C., Auvrignon, A., Bonnaure-Mallet, M., Duval, M., De Lumley, L., Hartmann, O., Mechinaud, F., Sirvent, N., Orbach, D., Doireau, V., Boutard, P., Dalle, J. H., Reguerre, Y., Pautard, B., Aubier, F., Schneider, P., Suc, A., Couillaut, G., … Pain task force of the SFCE (2007). Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. *Journal of pediatric hematology/oncology*, *29*(2), 86–94. https://doi.org/10.1097/MPH.0b013e318030a3e4

Sung, L., Tomlinson, G. A., Greenberg, M. L., Koren, G., Judd, P., Ota, S., & Feldman, B. M. (2007). Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients. *European journal of cancer (Oxford, England : 1990)*, *43*(8), 1269–1275. https://doi.org/10.1016/j.ejca.2007.02.001

Karolewska, E., Konopka, T., Pupek, M., Chybicka, A., & Mendak, M. (2008). Antibacterial potential of saliva in children with leukemia. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*, *105*(6), 739–744. https://doi.org/10.1016/j.tripleo.2007.10.010

Kuhn, A., Porto, F. A., Miraglia, P., & Brunetto, A. L. (2009). Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children. *Journal of pediatric hematology/oncology*, *31*(1), 33–37. https://doi.org/10.1097/MPH.0b013e318192cb8e

Cauwels, R. G., & Martens, L. C. (2011). Low level laser therapy in oral mucositis: a pilot study. *European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry*, *12*(2), 118–123. https://doi.org/10.1007/BF03262791

Cheng, K. K., Lee, V., Li, C. H., Goggins, W., Thompson, D. R., Yuen, H. L., & Epstein, J. B. (2011). Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. *Oral oncology*, *47*(3), 153–162. https://doi.org/10.1016/j.oraloncology.2010.11.019

Otmani, N., Alami, R., Hessissen, L., Mokhtari, A., Soulaymani, A., & Khattab, M. (2011). Determinants of severe oral mucositis in paediatric cancer patients: a prospective study. *International journal of paediatric dentistry*, *21*(3), 210–216. https://doi.org/10.1111/j.1365-263X.2011.01113.x

Rimulo, A. L., Ferreira, M. C., Abreu, M. H., Aguirre-Neto, J. C., & Paiva, S. M. (2011). Chemotherapy-induced oral mucositis in a patient with acute lymphoblastic leukaemia. *European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry*, *12*(2), 124–127. https://doi.org/10.1007/BF03262792

Bektaş-Kayhan, K., Küçükhüseyin, Ö., Karagöz, G., Ünür, M., Öztürk, O., Ünüvar, A., Devecioğlu, Ö., & Yilmaz-Aydoğan, H. (2012). Is the MDR1 C3435T polymorphism responsible for oral mucositis in children with acute lymphoblastic leukemia?. *Asian Pacific journal of cancer prevention : APJCP*, *13*(10), 5251–5255. https://doi.org/10.7314/apjcp.2012.13.10.5251

Cheng, K. K., Lee, V., Li, C. H., Yuen, H. L., & Epstein, J. B. (2012). Oral mucositis in pediatric and adolescent patients undergoing chemotherapy: the impact of symptoms on quality of life. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, *20*(10), 2335–2342. https://doi.org/10.1007/s00520-011-1343-1

Nielsen, B. N., Aagaard, G., Henneberg, S. W., Schmiegelow, K., Hansen, S. H., & Rømsing, J. (2012). Topical morphine for oral mucositis in children: dose finding and absorption. *Journal of pain and symptom management*, *44*(1), 117–123. https://doi.org/10.1016/j.jpainsymman.2011.06.029

Pels E. (2012). Oral mucositis in children suffering from acute lymphoblastic leukaemia. *Contemporary oncology (Poznan, Poland)*, *16*(1), 12–15. https://doi.org/10.5114/wo.2012.27331

Azher, U., & Shiggaon, N. (2013). Oral health status of children with acute lymphoblastic leukemia undergoing chemotherapy. *Indian journal of dental research : official publication of Indian Society for Dental Research*, *24*(4), 523. https://doi.org/10.4103/0970-9290.118371

Bardellini, E., Schumacher, F., Conti, G., Porta, F., Campus, G., & Majorana, A. (2013). Risk factors for oral mucositis in children receiving hematopoietic cell transplantation for primary immunodeficiencies: a retrospective study. *Pediatric transplantation*, *17*(5), 492–497. https://doi.org/10.1111/petr.12094

Inati, A., Akouri, G., & Abbas, H. A. (2013). A rare aggravation of severe mucositis post chemotherapy in a child with acute lymphoblastic leukemia. *F1000Research*, *2*, 196. https://doi.org/10.12688/f1000research.2-196.v1

Qutob, A. F., Allen, G., Gue, S., Revesz, T., Logan, R. M., & Keefe, D. (2013). Implementation of a hospital oral care protocol and recording of oral mucositis in children receiving cancer treatment : a retrospective and a prospective study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, *21*(4), 1113–1120. https://doi.org/10.1007/s00520-012-1633-2

Tomaževič, T., & Jazbec, J. (2013). A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. *Complementary therapies in medicine*, *21*(4), 306–312. https://doi.org/10.1016/j.ctim.2013.04.002

Ye, Y., Carlsson, G., Agholme, M. B., Wilson, J. A., Roos, A., Henriques-Normark, B., Engstrand, L., Modéer, T., & Pütsep, K. (2013). Oral bacterial community dynamics in paediatric patients with malignancies in relation to chemotherapy-related oral mucositis: a prospective study. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, *19*(12), E559–E567. https://doi.org/10.1111/1469-0691.12287

Chermetz, M., Gobbo, M., Ronfani, L., Ottaviani, G., Zanazzo, G. A., Verzegnassi, F., Treister, N. S., Di Lenarda, R., Biasotto, M., & Zacchigna, S. (2014). Class IV laser therapy as treatment for chemotherapy-induced oral mucositis in onco-haematological paediatric patients: a prospective study. *International journal of paediatric dentistry*, *24*(6), 441–449. https://doi.org/10.1111/ipd.12090

Didem, A., Ayfer, E., Ferda O. A. (2014). The effect of chewing gum on oral mucositis in children receiving chemotherapy. *Health Science Journal,* 8(3):373-382.

Ip, W. Y., Epstein, J. B., Lee, V., Yuen, H. L., Li, R., Thompson, D. R., Goggins, W. B., & Cheng, K. K. (2014). Oral mucositis in paediatric patients after chemotherapy for cancer. *Hong Kong medical journal = Xianggang yi xue za zhi*, *20 Suppl 7*, 4–8.

Yan L., You Y., Qi S., Xiaotong L., Fang W., Zhiyan L., Huaiping T., Ajing X., Jian Z. (2014). Association of ABCC2 224C.T Polymorphism with High-Dose Methotrexate Plasma Concentrations and Toxicities in Childhood Acute Lymphoblastic Leukemia. *PLoS ONE,* 9(1): e82681. doi:10.1371/journal.pone.0082681

Arrais Ribeiro I. L., Valença A. M. G., Bonan P. R. F., Carlo F. G. C. (2015). Oral monitoring of a pediatric patient during chemotherapy treatment. *Revista Cubana de Estomatología,* 52(2):196-201.

Soto, M., Lalla, R. V., Gouveia, R. V., Zecchin, V. G., Seber, A., & Lopes, N. N. (2015). Pilot study on the efficacy of combined intraoral and extraoral low-level laser therapy for prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation. *Photomedicine and laser surgery*, *33*(11), 540–546. https://doi.org/10.1089/pho.2015.3954

Amadori, F., Bardellini, E., Conti, G., Pedrini, N., Schumacher, R. F., & Majorana, A. (2016). Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study. *Lasers in medical science*, *31*(6), 1231–1236. https://doi.org/10.1007/s10103-016-1975-y

Bardellini, E., Amadori, F., Schumacher, R. F., D'Ippolito, C., Porta, F., & Majorana, A. (2016). Efficacy of a Solution Composed by Verbascoside, Polyvinylpyrrolidone (PVP) and Sodium Hyaluronate in the Treatment of Chemotherapy-induced Oral Mucositis in Children With Acute Lymphoblastic Leukemia. *Journal of pediatric hematology/oncology*, *38*(7), 559–562. https://doi.org/10.1097/MPH.0000000000000669

Bardellini, E., Amadori, F., & Majorana, A. (2016). Oral hygiene grade and quality of life in children with chemotherapy-related oral mucositis: a randomized study on the impact of a fluoride toothpaste with salivary enzymes, essential oils, proteins and colostrum extract versus a fluoride toothpaste without menthol. *International journal of dental hygiene*, *14*(4), 314–319. https://doi.org/10.1111/idh.12226

Kobya Bulut, H., & Güdücü Tüfekci, F. (2016). Honey prevents oral mocositis in children undergoing chemotherapy: A quasi-experimental study with a control group. *Complementary therapies in medicine*, *29*, 132–140. https://doi.org/10.1016/j.ctim.2016.09.018

Gholizadeh, N., Mehdipoor, M., Sajadi, H., & Moosavi, M. S. (2016). Palifermin and Chlorhexidine Mouthwashes in Prevention of Chemotherapy-Induced Mucositis in Children

with Acute Lymphocytic Leukemia: a Randomized Controlled Trial. *Journal of dentistry (Shiraz, Iran)*, *17*(4), 343–347.

Hamidieh, A. A., Sherafatmand, M., Mansouri, A., Hadjibabaie, M., Ashouri, A., Jahangard-Rafsanjani, Z., Gholami, K., Javadi, M. R., Ghavamzadeh, A., & Radfar, M. (2016). Calcitriol for Oral Mucositis Prevention in Patients With Fanconi Anemia Undergoing Hematopoietic SCT: A Double-Blind, Randomized, Placebo-Controlled Trial. *American journal of therapeutics*, *23*(6), e1700–e1708. https://doi.org/10.1097/MJT.0000000000000269

Lucchese, A., Matarese, G., Ghislanzoni, L. H., Gastaldi, G., Manuelli, M., & Gherlone, E. (2016). Efficacy and effects of palifermin for the treatment of oral mucositis in patients affected by acute lymphoblastic leukemia. *Leukemia & lymphoma*, *57*(4), 820–827. https://doi.org/10.3109/10428194.2015.1081192

Ávila-Sánchez C., Purizaca-Bazán J. P., Félix-Bermúdez G., Ellis-Irigoyen M. A., Vega-Vega M. L., Escamilla-Asiaín G. (2017). Impact of a protocol for the prevention and care of oral mucositis in pediatric patients diagnosed with cancer. *Mexical Journal of Oncology, 16(2):96-102* https://doi.org/10.24875/GAMO.17000049

Düzkaya, D. S., Uysal, G., Bozkurt, G., & Yakut, T. (2017). The Effect of Oral Care Using an Oral Health Care Guide on Preventing Mucositis in Pediatric Intensive Care. *Journal of pediatric nursing*, *36*, 98–102. https://doi.org/10.1016/j.pedn.2017.05.010

Medeiros-Filho, J. B., Maia Filho, E. M., & Ferreira, M. C. (2017). Laser and photochemotherapy for the treatment of oral mucositis in young patients: Randomized clinical trial. *Photodiagnosis and photodynamic therapy*, *18*, 39–45. https://doi.org/10.1016/j.pdpdt.2017.01.004

Pels E. J. (2017). Oral mucositis and saliva IgA, IgG and IgM concentration during anti-tumor treatment in children suffering from acute lymphoblastic leukemia. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University*, *26*(9), 1351–1358. https://doi.org/10.17219/acem/64940

Pourdeghatkar F., Motaghi M., Comparative effect of chamomile mouthwash and topical mouth rinse in prevention of chemotherapy-induced oral mucositis in Iranian pediatric patients with acute lymphoblastic leukemia. (2017). *Iranian Journal Of Blood And Cancer,* 9(3) 84-88

Ribeiro, I. L. A., Limeira, R. R. T., Dias de Castro, R., Ferreti Bonan, P. R., & Valença, A. M. G. (2017). Oral Mucositis in Pediatric Patients in Treatment for Acute Lymphoblastic Leukemia. *International journal of environmental research and public health*, *14*(12), 1468. https://doi.org/10.3390/ijerph14121468

Vitale, M. C., Modaffari, C., Decembrino, N., Zhou, F. X., Zecca, M., & Defabianis, P. (2017). Preliminary study in a new protocol for the treatment of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) and chemotherapy (CT). *Lasers in medical science*, *32*(6), 1423–1428. https://doi.org/10.1007/s10103-017-2266-y

Allen, G., Logan, R., Revesz, T., Keefe, D., & Gue, S. (2018). The Prevalence and Investigation of Risk Factors of Oral Mucositis in a Pediatric Oncology Inpatient Population; a Prospective Study. *Journal of pediatric hematology/oncology*, *40*(1), 15–21. https://doi.org/10.1097/MPH.0000000000000970

Arshadi Bostanabad M, Hiradfar Amirataollah, Mohammadpoorasl A, Javadzadeh Y, Khalvati B, Alvandnezhad T. The Effect of Mucoadhesive Gel Containing Satureja Hortensis Extract 1% on Severity of Chemotherapy-induced Mucositis Pain in Children: A Randomized Clinical Trial. Int J Pediatr 2018; 6(5): 7605-14. DOI: 10.22038/ijp.2017.25259.2143

Carreón-Burciaga, R. G., Castañeda-Castaneira, E., González-González, R., Molina-Frechero, N., Gaona, E., & Bologna-Molina, R. (2018). Severity of Oral Mucositis in Children following Chemotherapy and Radiotherapy and Its Implications at a Single Oncology Centre in Durango State, Mexico. *International journal of pediatrics*, *2018*, 3252765. https://doi.org/10.1155/2018/3252765

Damascena, L. C. L., de Lucena, N. N. N., Ribeiro, I. L. A., de Araujo, T. L. P., de Castro, R. D., Bonan, P. R. F., Lima Neto, E. A., de Araújo Filho, L. M., & Valença, A. M. G. (2018). Factors Contributing to the Duration of Chemotherapy-Induced Severe Oral Mucositis in Oncopediatric Patients. *International journal of environmental research and public health*, *15*(6), 1153. https://doi.org/10.3390/ijerph15061153

Funato, M., Ozeki, M., Suzuki, A., Ishihara, M., Kobayashi, R., Nozawa, A., Yasue, S., Endo-Ohnishi, S., Fukao, T., & Itoh, Y. (2018). Prophylactic Effect of Polaprezinc, a Zinc-L-carnosine, Against Chemotherapy-induced Oral Mucositis in Pediatric Patients Undergoing Autologous Stem Cell Transplantation. *Anticancer research*, *38*(8), 4691–4697. https://doi.org/10.21873/anticanres.12775

Gobbo, M., Verzegnassi, F., Ronfani, L., Zanon, D., Melchionda, F., Bagattoni, S., Majorana, A., Bardellini, E., Mura, R., Piras, A., Petris, M. G., Mariuzzi, M. L., Barone, A., Merigo, E., Decembrino, N., Vitale, M. C., Berger, M., Defabianis, P., Biasotto, M., Ottaviani, G., … Zanazzo, G. A. (2018). Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT. *Pediatric blood & cancer*, *65*(8), e27098. https://doi.org/10.1002/pbc.27098

Oosterom, N., Griffioen, P. H., den Hoed, M. A. H., Pieters, R., de Jonge, R., Tissing, W. J. E., van den Heuvel-Eibrink, M. M., & Heil, S. G. (2018). Global methylation in relation to

methotrexate-induced oral mucositis in children with acute lymphoblastic leukemia. *PloS one*, *13*(7), e0199574. https://doi.org/10.1371/journal.pone.0199574

Ribeiro da Silva, V. C., da Motta Silveira, F. M., Barbosa Monteiro, M. G., da Cruz, M. M. D., Caldas Júnior, A. F., & Pina Godoy, G. (2018). Photodynamic therapy for treatment of oral mucositis: Pilot study with pediatric patients undergoing chemotherapy. *Photodiagnosis and photodynamic therapy*, *21*, 115–120. https://doi.org/10.1016/j.pdpdt.2017.11.010

Ali, M. H. M., & Nurelhuda, N. M. (2019). Oral health status and its determinants in children with leukaemia at the Radiation and Isotope Center Khartoum, Khartoum State, Sudan. *Sudanese journal of paediatrics*, *19*(2), 93–100. https://doi.org/10.24911/SJP.106-1568288518

M. Alkhouli M., Laflouf M. (2019). Evaluation of the effectiveness of olive oil to prevent chemotherapy induced oral mucositis: A randomized controlled clinical trial. Pediatric Dental Journal, 29. 123-131, https://doi.org/10.1016/j.pdj.2019.08.001

Devi, K. S., & Allenidekania, A. (2019). The Relationship of Oral Care Practice at Home with Mucositis Incidence in Children with Acute Lymphoblastic Leukemia. *Comprehensive child and adolescent nursing*, *42*(sup1), 56–64. https://doi.org/10.1080/24694193.2019.1577926

Deyell, R. J., Wu, B., Rassekh, S. R., Tu, D., Samson, Y., Fleming, A., Bouffet, E., Sun, X., Powers, J., Seymour, L., Baruchel, S., & Morgenstern, D. A. (2019). Phase I study of vinblastine and temsirolimus in pediatric patients with recurrent or refractory solid tumors: Canadian Cancer Trials Group Study IND.218. *Pediatric blood & cancer*, *66*(3), e27540. https://doi.org/10.1002/pbc.27540

Hurrell, L., Burgoyne, L., Logan, R., Revesz, T., & Gue, S. (2019). The Management of Pediatric Oncology Inpatients With Oral Mucositis. *Journal of pediatric hematology/oncology*, *41*(8), e510–e516. https://doi.org/10.1097/MPH.0000000000001546

Kapoor, G., Goswami, M., Sharma, S., Mehta, A., & Dhillon, J. K. (2019). Assessment of oral health status of children with Leukemia: A cross-sectional study. *Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*, *39*(6), 564–571. https://doi.org/10.1111/scd.12419

Lucena, N. N. N., Damascena, L. C. L., Ribeiro, I. L. A., Lima-Filho, L. M. A., & Valença, A. M. G. (2019). The Contribution of Motor Changes to Oral Mucositis in Pediatric Cancer Patients: A Cross-Sectional Study. *International journal of environmental research and public health*, *16*(18), 3395. https://doi.org/10.3390/ijerph16183395

Noirrit-Esclassan E., Valera M.C., Vignes E., Munzer C., Bonal S., Daries ,M., Vaysse F., Puiseux C., Castex M. P., Boulanger C., Pasquet M. Photobiomodulation with a combination of two wavelengths in the treatment of oral mucositis in children: The PEDIALASE

feasibility study. *Archives de Pe´diatrie,* 26 (2019) 268–274. https://doi.org/10.1016/j.arcped.2019.05.012.

Oosterom, N., Dirks, N. F., Heil, S. G., de Jonge, R., Tissing, W. J. E., Pieters, R., van den Heuvel-Eibrink, M. M., Heijboer, A. C., & Pluijm, S. M. F. (2019). A decrease in vitamin D levels is associated with methotrexate-induced oral mucositis in children with acute lymphoblastic leukemia. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, *27*(1), 183–190. https://doi.org/10.1007/s00520-018-4312-0

Ribeiro, I., de Andrade Lima Neto, E., & Valença, A. M. (2019). Chemotherapy in Pediatric Oncology Patients and the Occurrence of Oral Mucositis. *International journal of clinical pediatric dentistry*, *12*(4), 261–267. https://doi.org/10.5005/jp-journals-10005-1633

Singh, R., Sharma, S., Kaur, S., Medhi, B., Trehan, A., & Bijarania, S. K. (2019). Effectiveness of Topical Application of Honey on Oral Mucosa of Children for the Management of Oral Mucositis Associated with Chemotherapy. *Indian journal of pediatrics*, *86*(3), 224–228. https://doi.org/10.1007/s12098-018-2733-x

Hans Christian, Margaretha Suharsini, Eva Fauziah. Effects of Probiotics on Clinical Appearance of Oral Mucositis in Children with Leukemia during Chemotherapy. Int J Dentistry Oral Sci. 2020;7(11):1032-1036. doi: http://dx.doi.org/10.19070/2377-8075-20000204

Costa, R. C., Bezerra, P. M. M., Damascena, L. C. L., Ribeiro, I. L. A., Bonan, P. R. F., de Sousa, S. A., Almeida, L. F. D., & Valença, A. M. G. (2020). Impact of Saliva and Cariogenic Microbiota on the Chemotherapy-Induced Oral Mucositis in Oncopediatric Patients: A Preliminary Longitudinal Study. *International journal of dentistry*, *2020*, 1243953. https://doi.org/10.1155/2020/1243953

Gutiérrez-Vargas, R., Villasis-Keever, M. Á., Portilla-Robertson, J., Ascencio-Montiel, I. D., & Zapata-Tarrés, M. (2020). Effect of zinc on oropharyngeal mucositis in children with acute leukemia undergoing chemotherapy. *Medicina oral, patologia oral y cirugia bucal*, *25*(6), e791–e798. https://doi.org/10.4317/medoral.23798

Immonen, E., Aine, L., Nikkilä, A., Parikka, M., Grönroos, M., Vepsäläinen, K., Palmu, S., Helminen, M., Peltomäki, T., & Lohi, O. (2020). Randomized controlled and double-blinded study of Caphosol versus saline oral rinses in pediatric patients with cancer. *Pediatric blood & cancer*, *67*(10), e28520. https://doi.org/10.1002/pbc.28520

Kamsvåg, T., Svanberg, A., Legert, K. G., Arvidson, J., von Essen, L., Mellgren, K., Toporski, J., Winiarski, J., & Ljungman, G. (2020). Prevention of oral mucositis with cryotherapy in children undergoing hematopoietic stem cell transplantations-a feasibility study and randomized controlled trial. *Supportive care in cancer : official journal of the*

Multinational Association of Supportive Care in Cancer, *28*(10), 4869–4879. https://doi.org/10.1007/s00520-019-05258-2

Mubaraki, S., Pani, S. C., Alseraihy, A., Abed, H., & Alkhayal, Z. (2020). The efficacy of two different oral hygiene regimens on the incidence and severity of oral mucositis in pediatric patients receiving hematopoietic stem cell transplantation: A prospective interventional study. *Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*, *40*(6), 566–573. https://doi.org/10.1111/scd.12525

Nunes, L. F. M., de Arruda, J. A. A., Souza, A. F., Silva, R. C. C., Lanza, C. R. M., Kakehasi, F. M., Mesquita, R. A., Abreu, L. G., Travassos, D. V., & Silva, T. A. (2020). Prophylactic photobiomodulation therapy using 660 nm diode laser for oral mucositis in paediatric patients under chemotherapy: 5-year experience from a Brazilian referral service. *Lasers in medical science*, *35*(8), 1857–1866. https://doi.org/10.1007/s10103-020-03060-9

Parra, J. J., Alvarado, M. C., Monsalve, P., Costa, A. L. F., Montesinos, G. A., & Parra, P. A. (2020). Oral health in children with acute lymphoblastic leukaemia: before and after chemotherapy treatment. *European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry*, *21*(1), 129–136. https://doi.org/10.1007/s40368-019-00454-4

Pires HF, Bezerra PMM, Silva VB, Ribeiro ILA, Serpa EBM, Sousa SA, et al. Occurrence and severity of oral mucositis in Brazilian pediatric cancer patients. Pesqui Bras Odontopediatria Clín Integr. 2020; 20:e5621. https://doi.org/10.1590/pboci.2020.085

Prakash, S., Meena, J. P., Gupta, A. K., Bakhshi, S., Velpandian, T., Pandey, R. M., & Seth, R. (2020). Ketamine mouthwash versus placebo in the treatment of severe oral mucositis pain in children with cancer: A randomized double-blind placebo-controlled trial. *Pediatric blood & cancer*, *67*(9), e28573. https://doi.org/10.1002/pbc.28573

Proc, P., Szczepańska, J., Zubowska, M., Wyka, K., & Młynarski, W. (2020). Salivary immunoglobulin A level during steroids and chemotherapy treatment administered in remission induction phase among pediatric patients with acute lymphoblastic leukemia. *Medicine*, *99*(42), e22802. https://doi.org/10.1097/MD.0000000000022802

Sajith, M., Pawar, A., Bafna, V., Bartakke, S., Subramanian, K., & Vaidya, N. (2020). Serum Methotrexate Level and Side Effects of High Dose Methotrexate Infusion in Pediatric Patients with Acute Lymphoblastic Leukaemia (ALL). *Indian journal of hematology & blood transfusion : an official journal of Indian Society of Hematology and Blood Transfusion*, *36*(1), 51–58. https://doi.org/10.1007/s12288-019-01144-3

Alkhouli, M., Laflouf, M., & Comisi, J. C. (2021). Assessing the topical application efficiency of two biological agents in managing chemotherapy-induced oral mucositis in

children: A randomized clinical trial. *Journal of oral biology and craniofacial research*, *11*(3), 373–378. https://doi.org/10.1016/j.jobcr.2021.04.001

Alkhouli, M., Laflouf, M., & Alhaddad, M. (2021). Efficacy of Aloe-Vera Use for Prevention of Chemotherapy-Induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia: A Randomized Controlled Clinical Trial. *Comprehensive child and adolescent nursing*, *44*(1), 49–62. https://doi.org/10.1080/24694193.2020.1727065

Attinà, G., Romano, A., Maurizi, P., D'Amuri, S., Mastrangelo, S., Capozza, M. A., Triarico, S., & Ruggiero, A. (2021). Management of Oral Mucositis in Children With Malignant Solid Tumors. *Frontiers in oncology*, *11*, 599243. https://doi.org/10.3389/fonc.2021.599243

Bezerra, P. M. M., Sampaio, M. E. A., Dos Santos, F. G., Ribeiro, I. L. A., Santiago, B. M., de Sousa, S. A., & Valença, A. M. G. (2021). The effectiveness of an oral health education and prevention program on the incidence and severity of oral mucositis in pediatric cancer patients: a non-randomized controlled study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, *29*(12), 7877–7885. https://doi.org/10.1007/s00520-021-06387-3

Curra, M., Gabriel, A. F., Ferreira, M. B. C., Martins, M. A. T., Brunetto, A. T., Gregianin, L. J., & Martins, M. D. (2021). Incidence and risk factors for oral mucositis in pediatric patients receiving chemotherapy. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, *29*(11), 6243–6251. https://doi.org/10.1007/s00520-021-06199-5

Guimaraes, D. M., Ota, T. M. N., Da Silva, D. A. C., Almeida, F. L. D. S., Schalch, T. D., Deana, A. M., Junior, J. M. A., & Fernandes, K. P. S. (2021). Low-level laser or LED photobiomodulation on oral mucositis in pediatric patients under high doses of methotrexate: prospective, randomized, controlled trial. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, *29*(11), 6441–6447. https://doi.org/10.1007/s00520-021-06206-9

Guimarães, J. R., Carvalho, L. G., Damascena, L. C., Sampaio, M. E., Ribeiro, I. L., Sousa, S. A., & Valença, A. M. (2021). The incidence of severe oral mucositis and its occurrence sites in pediatric oncologic patients. *Medicina oral, patologia oral y cirugia bucal*, *26*(3), e299–e303. https://doi.org/10.4317/medoral.24185

Otmani, N., & Hattad, S. (2021). Clinical Outcome in Children with Chemotherapy-Induced Mucositis. *Seminars in oncology nursing*, *37*(3), 151160. https://doi.org/10.1016/j.soncn.2021.151160

Viana Filho, J. M. C., Coêlho, M. C., Ribeiro, I. L. A., Persuhn, D. C., Valença, A. M. G., & Oliveira, N. F. P. (2021). ABCG2 polymorphism, age and leukocyte count may contribute to

oral mucositis in oncopediatric patients. *Brazilian dental journal*, *32*(2), 14–26. https://doi.org/10.1590/0103-6440202103768

Bardellini, E., Amadori, F., Veneri, F., Albini, G., Porta, F., & Alessandra, M. (2023). Dysphagia-related mucositis in children undergoing chemotherapy: The COMEDY pattern. *Oral diseases*, *29*(7), 2705–2709. https://doi.org/10.1111/odi.14344

Coêlho, M. C., Viana Filho, J. M. C., Souza, B. F., Valença, A. M. G., Persuhn, D. C., & Oliveira, N. F. P. (2022). Genetic polymorphisms of genes involved in oxidative stress and inflammatory management in oncopediatric patients with chemo-induced oral mucositis. *Journal of applied oral science : revista FOB*, *30*, e20210490. https://doi.org/10.1590/1678-7757-2021-0490

Fiwek, P., Emerich, K., Irga-Jaworska, N., & Pomiecko, D. (2022). Photobiomodulation Treatment in Chemotherapy-Induced Oral Mucositis in Young Haematological Patients-A Pilot Study. *Medicina (Kaunas, Lithuania)*, *58*(8), 1023. https://doi.org/10.3390/medicina58081023

Hassan, H., Kinsey, S., & Phillips, B. (2022). Mucositis reduction with probiotics in children with cancer: a randomised-controlled feasibility study. *Archives of disease in childhood*, *107*(3), 259–264. https://doi.org/10.1136/archdischild-2020-319968

Massano, D., Paratella, A., Affinita, M. C., De Salvo, G. L., Petrangolini, G., Riva, A., & Bisogno, G. (2022). Administration of Samital® in children with oral mucositis: a feasibility study. *European review for medical and pharmacological sciences*, *26*(22), 8576–8581. https://doi.org/10.26355/eurrev_202211_30393

Miranda-Silva, W., da Fonseca, F. P., Gomes, A. A., Mafra, A. B. B., Rocha, V., & Fregnani, E. R. (2022). Oral mucositis in paediatric cancer patients undergoing allogeneic hematopoietic stem cell transplantation preventively treated with professional dental care and photobiomodulation: Incidence and risk factors. *International journal of paediatric dentistry*, *32*(2), 251–263. https://doi.org/10.1111/ipd.12850

Ludovichetti, F. S., Costa, G., Signoriello, A. G., Stellini, E., Zerman, N., Biffi, A., & Mazzoleni, S. (2023). Evaluating high power laser therapy (HPLT) as treatment for chemotherapy-induced oral mucositis in paediatric patients with oncohematological diseases. *International journal of paediatric dentistry*, *33*(3), 269–277. https://doi.org/10.1111/ipd.13050

Cheng, K. K., Molassiotis, A., Chang, A. M., Wai, W. C., & Cheung, S. S. (2001). Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. *European journal of cancer (Oxford, England : 1990)*, *37*(16), 2056–2063. https://doi.org/10.1016/s0959-8049(01)00098-3

Badr, L. K., El Asmar, R., Hakim, S., Saad, R., Merhi, R., Zahreddine, A., & Muwakkit, S. (2023). The efficacy of honey or olive oil on the severity of oral mucositis and pain compared to placebo (standard care) in children with leukemia receiving intensive chemotherapy: A randomized controlled trial (RCT). *Journal of pediatric nursing*, *70*, e48–e53. https://doi.org/10.1016/j.pedn.2022.12.003

de Souza, B. F., Viana Filho, J. M. C., de Queiroz Neto, J. N., Coêlho, M. C., Valença, A. M. G., Persuhn, D. C., & de Oliveira, N. F. P. (2023). DNA Methyltransferase Genes Are Associated with Oral Mucositis and Creatinine Levels in Oncopediatric Patients. *Genes*, *14*(6), 1136. https://doi.org/10.3390/genes14061136

Fiwek, P.; Irga-Jaworska, N.; Wojtylak, S.; Biernat, W.; Emerich, K.; Pomiecko, D. Assessment of Cytological Changes in the Oral Mucosa in Young Hematological Patients Treated with Systemic Chemotherapy. J. Clin. Med. 2023, 12, 2665. https://doi.org/10.3390/jcm12072665

Lohakare, T., Kumari, D., Wanjari, M. B., Maurya, A., Kurian, B., & Meshram, K. M. (2023). Effectiveness of Application of Oral Regimen, Practicing Oral Health, Health Education, Observation (APHO) Nursing Intervention in Preventing and Managing Oral Mucositis in Children Undergoing Chemotherapy: An Interventional Study in Central India. *Cureus*, *15*(6), e40902. https://doi.org/10.7759/cureus.40902

Sampaio, M. E. A., Bezerra, P. M. M., Santos, F. G. D., Ribeiro, I. L. A., Sousa, S. A., Santiago, B. M., & Valença, A. M. G. (2024). A hospital-based oral health education program impacts in pediatric cancer patients-A pilot study. *Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*, *44*(1), 196–205. https://doi.org/10.1111/scd.12847

Eduardo, F.deP., Bezinelli, L. M., de Carvalho, D. L., Lopes, R. M., Fernandes, J. F., Brumatti, M., Vince, C. S., de Azambuja, A. M., Vogel, C., Hamerschlak, N., & Correa, L. (2015). Oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation: clinical outcomes in a context of specialized oral care using low-level laser therapy. *Pediatric transplantation*, *19*(3), 316–325. https://doi.org/10.1111/petr.12440

Lauritano, D., Petruzzi, M., Di Stasio, D., & Lucchese, A. (2014). Clinical effectiveness of palifermin in prevention and treatment of oral mucositis in children with acute lymphoblastic leukaemia: a case-control study. *International journal of oral science*, *6*(1), 27–30. https://doi.org/10.1038/ijos.2013.93

Yavuz, B., & Bal Yılmaz, H. (2015). Investigation of the effects of planned mouth care education on the degree of oral mucositis in pediatric oncology patients. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses*, *32*(1), 47–56. https://doi.org/10.1177/1043454214554011

Abdulrhman, M., Elbarbary, N. S., Ahmed Amin, D., & Saeid Ebrahim, R. (2012). Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: a randomized controlled pilot study. *Pediatric hematology and oncology*, *29*(3), 285–292. https://doi.org/10.3109/08880018.2012.669026

Al Jaouni, S. K., Al Muhayawi, M. S., Hussein, A., Elfiki, I., Al-Raddadi, R., Al Muhayawi, S. M., Almasaudi, S., Kamal, M. A., & Harakeh, S. (2017). Effects of Honey on Oral Mucositis among Pediatric Cancer Patients Undergoing Chemo/Radiotherapy Treatment at King Abdulaziz University Hospital in Jeddah, Kingdom of Saudi Arabia. *Evidence-based complementary and alternative medicine : eCAM*, *2017*, 5861024. https://doi.org/10.1155/2017/5861024

Appendix 4. General and demographic characteristics of the cases of oral mucositis in the present systematic review.

Author	Country	Study Design	Sample	Mean age	Tumor Types
Lever et al., 1987	Canada	RCT	4 (50% boys and 50% girls)	7.5	HM and ST
Levy-Polack et al., 1998	Argentina	PC	96 (54.1% boys and 45.8% girls)	8.5	HM
Estlin et al., 2001	USA	RCT	16 (43.7% boys and 56.2 girls)	9	HM and ST
Cheng et al., 2002	Hong Kong	PC	14 (92.8% boys and 7.1 girls)	11	HM and ST
Cheng et al., 2003	Hong Kong	RCT	34 (61.7% boys and 38.2% girls)	11	HM and ST
Chen et al., 2004	Taiwan	QE	30	9.5	HM
Cheng et al., 2004	Hong Kong	RCT	35 (60% boys and 40% girls)	11.5	HM and ST
Schmid et al., 2006	Germany	RCT	30 (60% boys and 40% girls)	9.5	HM and ST

Bechard et al., 2007	USA	PC	37 (45.9% boys and 54.05% girls)	9.1	HM
Cruz et al., 2007	Brazil	RCT	60 (65% boys and 35% girls)	10.5	HM and ST
Cubukcu et al., 2007	Turkey	RCT	40 (65% boys and 35% girls)	7.5	HM and ST
de Koning et al., 2007	Amsterdam	RCT	25 (68% boys and 32% girls)	7.5	HM and ST
El -Housseiny et al., 2007	Egypt	PC	150 (54.6% boys and 45.3% girls)	6	HM
El-Housseiny et al., 2007	Egypt	RCT	63	6	Not informed
Gandemer et al., 2007	France	RCT	145 (64.1% boys and 35.8% girls)	11.5	HM and ST

Sung et al., 2007	Canada	RCT	16 (62.5% boys and 37.5% girls)	10.5	HM and ST
Karolewska et al., 2008	Poland	CC	44 (56.9% boys and 43.1% girls)	10	HM
Kuhn et al., 2009	Brazil	RCT	21 (80.9% boys and 19% girls)	8.2	HM and ST
Cauwels et al., 2011	Belgium	RCT	16 (50% boys and 50% girls)	9.4	HM and ST
Cheng et al., 2011	Singapore	PC	140 (62.8% boys and 37.1% girls)	12	HM and ST
Otmani et al., 2011	Morocco	PC	970 (63.8% boys and 36.1% girls)	8	HM and ST
Rimulo et al., 2011	Brazil	CR	1 (100% girl)	5	HM
Bektaş-Kayhan et al., 2012	Turkey	CC	115 (66.9 boys and 33.0% girls)	patients and controls were 8.68 and 10.14	HM
Cheng et al., 2012	Singapore	RC	140 (62.8 boys and 37.1% girls)	12	HM and ST

Nielsen et al., 2012	Denmark	QE	12 (66.6% boys and 33.3% girls)	9.5	HM
Pels et al., 2012	Poland	PC	78	10	HM
Azher et al., 2013	India	PC	94	8	HM
Bardellini et al., 2013	Italy	RC	55 (63.6% boys and 36.3% girls)	6	HM
Inati et al., 2013	Lebanon	CR	1 (100% girl)	5	HM
Qutob et al., 2013	Australia	PC	97	8	HM and ST
Tomazevic et al., 2013	Slovenia	RCT	40 (50% boys and 50% girls)	9.5	HM and ST
Ye et al., 2013	Sweden	PC	37 (75.6% boys and 24.3% girls)	10.3	HM and ST
Chermetz et al., 2014	Italy	PC	18 (66.6% boys and 33.3% girls)	13.5	HM and ST

Didem et al., 2014	Turkey	CC	60 (48.3% boys 51.6% girls)	12	HM and ST
Ip et al., 2014	China	PC	140 (62.8% boys and 37.1% girls)	12	HM and ST
Liu et al., 2014	China	QE	112 (52.6% boys and 47.3% girls)	5.5	HM (ALL)
Lima Arrais Ribeiro et al., 2015	Brazil	CR	1 (100% boy)	5.5	HM (HL)
Soto et al., 2015	Brazil	CC	24 (70.8% boys and 29.1 girls)	9	HM and ST
Amadori et al., 2016	Italy	RCT	123	10.5	HM and ST
Bardellini et al., 2016	Italy	RCT	59 (25 boys and 34 girls)	Not informed	HM
Bardellini et al., 2016	Italy	RCT	64 (35.9% boys and 64.0% girls)	10	HM
Bulut et al., 2016	Turkey	CC	76 (50% boys and 50% girls)	12	HM

Gholizadeh et al., 2016	Iran	RCT	90 (48.8% boys and 51.1% girls)	11.5	HM
Hamidieh et al., 2016	Iran	RCT	28 (82.1% boys and 17.8% girls)	7.5	HM
Lucchese et al., 2016	Italy	RCT	54 (48.1% boys and 51.8% girls)	11.5	HM
Ávila-Sánchez et al., 2017	Mexico	RC	157 (79.6% boys and 19.7% girls)	7.9	HM and ST
Duzkaya et al., 2017	Turkey	PC	594 (53.7% boys and 46.2% girls)	8.5	Not informed
Medeiros-Filho et al., 2017	Brazil	RCT	15 (93.3% boys and 6.6% girls)	9.5	HM and ST
Pels et al., 2017	Poland	CC	78 (56.4% boys and 43.5% girls)	10	HM

Pourdeghatkar et al., 2017	Iran	RCT	62 (56.4% boys and 43.5% girls)	10.5	HM
Ribeiro et al., 2017	Brazil	PC	42 (45.2% boys and 54.7% girls)	10	HM
Vitale et al., 2017	Italy	RCT	16	10.5	Not informed
Allen et al., 2018	Australia	PC	73	Not informed	HM and ST
Bostanabad et al., 2018	Iran	RCT	60 (66.6% boys and 33.3% girls)	8,5	HM and ST
Carreón-Burciaga et al., 2018	Mexico	RC	51 (58.82% boys and 41.1% girls)	7	HM and ST
Damascena et al., 2018	Brazil	RC	73 (52.0% boys and 47.9% girls)	9.5	HM and ST
Funato et al., 2018	Japan	RC	16 (56.2% boys and 43.7 girls)	9.5	ST
Gobbo et al., 2018	Italy	RCT	101 (53.4% boys and 46.5% girls)	10.5	HM and ST

Oosterom et al., 2018	The Netherlands	PC	82 (43.9% boys and 56.0% girls)	9.5	HM
Ribeiro da Silva et al., 2018	Brazil	RCT	29 (51.7% boys and 48.2% girls)	9	HM and ST
Ali et al., 2019	Sudan	CS	87 (60.9% boys and 39.0% girls)	7	HM
Alkhouli et al., 2019	Syria	RCT	22 (54.5% boys and 45.4% girls)	5	HM
Devi et al., 2019	Indonesia	CS	34 (58.8% boys and 41.1% girls)	7.5	HM
Deyell et al., 2019	Canada	QE	6 (83.3% boys and 16.6% girls)	13	ST
Hurrell et al., 2019	Australia	PC	47 (63.8% boys and 36.1% girls)	8.8	HM and ST
Kapoor et al., 2019	India	CS	220	8.5	HM
Lucena et al., 2019	Brazil	CS	70 (54.2% boys and 45.7% girls)	10.5	HM and ST

Noirrit-Esclassan et al., 2019	France	QE	22 (59.0% boys and 40.9% girls)	10	HM and ST
Oosterom et al., 2019	The Netherlands	PC	99 (44.4% boys and 55.5% girls)	10	HM
Ribeiro et al., 2019	Brazil	PC	105 (54.2% boys and 45.7% girls)	9.5	HM and ST
Singh et al., 2019	India	PC	100	Not informed	Not informed
Christian et al., 2020	Indonesia	QE	11	Not informed	HM
Costa et al., 2020	Brazil	PC	26 (42.3% boys and 57.6% girls)	11	HM and ST
Gutiérrez-Vargas et al., 2020	Mexico	QE	61 (59.0% boys and 40.9% girls)	12	HM
Immonen et al., 2020	Finland	RCT	45 (55.5% boys and 44.4% girls)	9.5	HM and ST

Kamsvåg et al,. 2020	Sweden	RCT	49 (53.0% boys and 46.9% girls)	10.5	HM and ST
Mubaraki et al., 2020	Saudi Arabia	RCT	45 (20 boys 25 girls)	8.5	HM
Nunes et al., 2020	Brazil	RC	148 (55.4% boys and 44.5% girls)	8.5	HM and ST
Parra et al., 2020	Ecuador	QE	32 (46.8% boys and 53.1% girls)	7	HM
Pires et al., 2020	Brazil	PC	85 (50.5% boys and 49.4% girls)	9.5	HM and ST
Prakash et al., 2020	India	RCT	44 (79.5% boys and 20.4% girls)	13	HM and ST
Proc et al., 2020	Poland	PC	24 (54.1% boys and 45.8% girls)	10.5	HM
Sajith et al., 2020	India	PC	62 (72.5% boys and 27.4% girls)	9.5	HM
Alkhouli et al., 2021	Syria	RCT	36 (47.22% boys and 52.7% girls)	7.5	HM

Alkhouli et al., 2021	Syria	RCT	22 (50% boys and 50% girls)	4.5	HM
Attina et al., 2021	Italy	RC	84 (43 boys and 41 girls)	11	HM and ST
Bezerra et al., 2021	Brazil	PC	28 (57.1% boys and 42.8% girls)	10	HM and ST
Curra et al., 2021	Brazil	PC	112 (54.4% boys and 45.5% girls)	8.5	HM and ST
Guimaraes et al., 2021	Brazil	RCT	80	8	HM
Guimaraes et al., 2021	Brazil	RC	56	8.5	HM and ST
Otmani et al., 2021	Morocco	PC	46 (50% boys and 50% girls)	9	HM and ST
Viana Filho et al., 2021	Brazil	RC	64 (56.2% boys and 43.7% girls)	10.5	HM

Bardellini et al., 2022	Italy	RC	42 (54.7% boys and 45.2% girls)	9	HM and ST
Coelho et al., 2022	Brazil	CS	95 (56.8% boys and 43.1% girls)	11	HM
Fiwek et al., 2022	Poland	RCT	23 (39.1% boys and 60.8% girls)	10.5	HM
Hassan et al., 2022	United Kingdon	RCT	10 (50% boys and 50% girls)	8	HM and ST
Massano et al., 2022	Italy	QE	18 (66.6% boys and 33.3% girls)	10	HM and ST
Miranda-Silva et al., 2022	Brazil	RC	49 (77.5% boys and 22.4% girls)	8.5	HM
Ludovichetti et al., 2023	Italia	PC	14 (42.8% boys and 57.1% girls)	10.5	HM

Bezinelli et al., 2015	Brazil	CC	51	9	HM
Lauritano et al., 2013	Italy	CC	40 (52.5% boys and 47.5% girls)	11.5	HM
Yavuz et al., 2014	Turkey	PC	16 (31.2% boys and 68.7% girls)	13	HM
Cheng et al., 2001	China	PC	42 (73.8% boys and 26.1% girls)	11	HM and ST
Badr et al 2023	Lebanon	RCT	42 (54.7% boys and 45.2%)	11	HM
de Souza et al 2023	Brazil	PC	85 (45.8% boys and 54.1% girls)	11.5	HM
Fiwek et al. 2023	Poland	PC	59 (61% boys and 38.9% girls)	10.5	HM
Lohakare et al., 2023	India	QI	45 (60% boys and 40% girls)	6.5	HM and ST

Sampaio et al., 2023	Brazil	QI	27 (51.8% boys and 48.1% girls)	11	HM and ST
Abdulrhmanm et al., 2012	Egypt	RCT	90 (63.3% boys and 36.6% girls)	10	HM
Al Jaouni et al., 2027	Saudi Arabia	RCT	40 (52.5% boys and 47.5% girls)	9.5	HM and ST

CC: case control; RCT: randomized clinical trial; CR: case report; PC: prospective cohort; RC: retrospective cohort; CS: cross sectional; HM: Hematological malignancies; ST: Solid tumors.

Appendix 5. Frequency of Oral Mucositis scales or Patient-Related Outcome Measures (PROMs) in each study.

	Scales								PROMs			
Author	**WHO**	**OAG**	**m-OAG**	**OMAS**	**Sonis Scale**	**OMQoL**	**ChiMES**	**CTC**	**NN**	**OMDQ MTS**	**PROM without specification**	**Scales/PROMs per study**
Lever et al., 1987									X			1
Levy-Polack et al., 1998									X			1
Estlin et al., 2001								X				1
Cheng et al., 2002		X										1

Cheng et al., 2003	X			1
Chen et al., 2004		X		1
Cheng et al., 2004		X		1
Schmid et al., 2006	X			1
Bechard et al., 2007			X	1
Cruz et al., 2007			X	1

Cubukcu et al., 2007	X			1
de Koning et al., 2007	X			1
El -Housseiny et al., 2007	X			1
El-Housseiny et al., 2007	X			1
Gandemer et al., 2007	X			1
Sung et al., 2007	X	X	X	3

Karolewska et al., 2008	X				1
Kuhn et al., 2009			X		1
Cauwels et al., 2011	X				1
Cheng et al., 2011				X	1
Otmani et al., 2011	X				1
Rimulo et al., 2011	X				1

Bektaş-Kayhan et al., 2012	X			1
Cheng et al., 2012			X	1
Nielsen et al., 2012	X			1
Pels et al., 2012	X			1
Azher et al., 2013	X			1
Bardellini et al., 2013	X			1
Inati et al., 2013	X			1

Qutob et al., 2013	X				X		2
Tomazevic et al., 2013		X					1
Ye et al., 2013	X						1
Chermetz et al., 2014	X						1
Didem et al., 2014	X	X					2
Ip et al., 2014			X			X	2
Liu et al., 2014				X			1

Lima Arrais Ribeiro et al., 2015		X			1
Soto et al., 2015				X	1
Amadori et al., 2016	X				1
Bardellini et al., 2016	X				1
Bardellini et al., 2016	X				1
Bulut et al., 2016	X				1

Gholizadeh et al., 2016	X			1
Hamidieh et al., 2016	X			1
Lucchese et al., 2016	X		X	2
Ávila-Sánchez et al., 2017	X			1
Duzkaya et al., 2017	X			1
Medeiros-Filho et al., 2017	X			1
Pels et al., 2017	X			1

Pourdeghatkar et al., 2017	X				1
Ribeiro et al., 2017		X			1
Vitale et al., 2017				X	1
Allen et al., 2018	X		X		2
Bostanabad et al., 2018	X				1
Carreón-Burciaga et al., 2018	X				1

Damascena et al., 2018		X			1
Funato et al., 2018	X				1
Gobbo et al., 2018	X				1
Oosterom et al., 2018				X	1
Ribeiro da Silva et al., 2018	X		X		2
Ali et al., 2019	X				1
Alkhouli et al., 2019	X				1

Devi et al., 2019		X			1
Deyell et al., 2019				X	1
Hurrell et al., 2019	X		X		2
Kapoor et al., 2019	X				1
Lucena et al., 2019		X			1
Noirrit-Esclassan et al., 2019	X				1

Oosterom et al., 2019				X	1
Ribeiro et al., 2019			X		1
Singh et al., 2019	X				1
Christian et al., 2020		X			1
Costa et al., 2020		X			1
Gutiérrez-Vargas et al., 2020	X				1

Immonen et al., 2020	X		X		X	3
Kamsvåg et al., 2020	X		X			2
Mubaraki et al., 2020	X					1
Nunes et al., 2020	X					1
Parra et al., 2020	X					1
Pires et al., 2020		X				1

Prakash et al., 2020	X			1
Proc et al., 2020			X	1
Sajith et al., 2020			X	1
Alkhouli et al., 2021	X			1
Alkhouli et al., 2021	X			1
Attina et al., 2021	X			1
Bezerra et al., 2021		X		1

Curra et al., 2021	X		1
Guimaraes et al., 2021	X		1
Guimaraes et al., 2021		X	1
Otmani et al., 2021		X	1
Viana Filho et al., 2021		X	1
Bardellini et al., 2022	X		1

Coelho et al., 2022		X			1
Fiwek et al., 2022	X			X	2
Hassan et al., 2022				X	1
Massano et al., 2022	X				1
Miranda-Silva et al., 2022	X				1
Ludovichetti et al., 2023	X				1

Bezinelli et al., 2015	X				1
Lauritano et al., 2013	X				1
Yavuz et al., 2014	X			X	2
Cheng et al., 2001		X			1
Badr, L. K., 2023.	X				1
de Souza, B. F., 2023			X		1
Fiwek, P., 2023	X				1

Lohakare, T., 2023	X			1
Sampaio, M. E. A., 2023		X		1
Abdulrhmanm, M., 2012			X	1
Al Jaouni, S. K, 2017	X			1

WHO: World Health Organization; OAG: Oral Assessment Guide; m-OAG: Modified Oral Assessment Guide; OMAS: Oral Mucositis Assessment Scale; OMQoL: Oral Mucositis Daily Questionnaire and Oropharyngeal Mucositis Quality of Life Scale; ChiMES: Children's International Mucositis Evaluation Scale; CTC: Common Toxicity Criteria (CTC); NN: Not nominated; OMDQ MTS: Self-report Mouth and Throat Soreness-Related Questions of the Oral Mucositis Daily Questionnaire.

Appendix 6. JBI Critical Appraisal Checklist of Cohort studies.

Author(s) (year of publication)	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilized?	Was appropriate statistical analysis used?
Bechard, L. J et al., 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Cheng, K. K et al., 2011	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No, yes	Yes	Yes
Ye, Y., et al.. 2013	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Ip, W. Y. et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Oosterom, N. et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Hurrell, L. et al., 2019	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Curra, M. et al., 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Levy-Polack, M. P. et al., 1998	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	No	Yes
Cheng, K. K. F. et al., 2002	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	No	Yes

Otmani, N. et al., 2011	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Qutob, A. F. et al., 2013	Yes	Unclear	Yes	No	No	Yes	Yes	Unclear	Yes	No	No
Chermetz, M. et al., 2014	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Duzkaya, D. et al., 2017	No	No	Yes	No	No	Yes	Yes	Yes	No, yes	No	Yes
Allen, G et al., 2018	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Oosterom, N et al., 2019	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Ribeiro, I. et al., 2019	No	No	Yes	No	No	Yes	Yes	Yes	No, yes	Yes	Yes
Costa, R. C. et al., 2020	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Pires, H. D. et al., 2020	No	No	Yes	No	No	No	Yes	Yes	No, yes	No	Yes
Proc, P. et al., 2020	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Sajith, M. et al., 2020	No	No	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Otmani, N et al., 2021	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Ludovichetti, F. S. et al., 2023	No	No	Yes	No	No	No	Yes	Yes	No, yes	Yes	Yes
Cheng, K.K, et al., 2001	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes

El -Housseiny et al., 2007	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Pels et al., 2012	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No
Azher et al., 2013	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	No	Yes
Singh et al., 2019	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Yavuz et al., 2014	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Unclear	No	Yes
Cheng et al., 2012	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Bardellini et al., 2013	Yes	Yes	Yes	No	No	No	Yes	Yes	No, yes	Yes	Yes
Ávila-Sánchez et al., 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	No	Yes
Carreón-Burciaga et al., 2018	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Unclear	No	Yes
Damascena et al., 2018	Yes	Yes	Yes	No	No	No	Yes	Yes	Unclear	No	Yes
Funato et al., 2018	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No, yes	Yes	Yes
Nunes et al., 2020	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Attina et al., 2021	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Viana Filho et al., 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes

Bardellini et al., 2022	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Miranda-Silva et al., 2022	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Ribeiro et al., 2017	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No, yes	No	Yes
Guimaraes j et al., 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
de Souza et al 2023	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Fiwek et al. 2023	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Unclear	No	Yes

Appendix 6. JBI Critical Appraisal Checklist of Quasi-experimental studies.

Author(s) (year of publication)	Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Were the participants included in any comparisons similar?	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Was there a control group?	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Was appropriate statistical analysis used?
Chen, C. F. et al., 2004	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Nielsen et al., 2012	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Liu et al., 2014	Yes	Yes	No	No	No	Unclear	Yes	Yes	Yes
Deyell et al., 2019	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Noirrit-Esclassan et al., 2019	Yes	Yes	No	Yes	No	Unclear	Yes	Yes	No
Christian et al., 2020	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Gutiérrez-Vargas et al., 2020	Yes	Yes	No	Yes	No	No, yes	Yes	Yes	Yes
Parra et al.,	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes

2020									
Massano et al., 2022	Yes	Yes	No	No	No	No, yes	Yes	Yes	Yes
Bulut et al., 2016	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Didem et al., 2014	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Bezerra et al., 2021	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Cauwels et al., 2011	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Lohakare et al., 2023	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Sampaio et al., 2023	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes

Appendix 6. JBI Critical Appraisal Checklist of randomized clinical trial:

Author(s) (year of publication)	Was true randomization used for assignment of participants to treatment groups?	Was allocation to treatment groups concealed?	Were treatment groups similar at the baseline?	Were participants blind to treatment assignment?	Were those delivering treatment blind to treatment assignment?	Were outcomes assessors blind to treatment assignment?	Were treatment groups treated identically other than the intervention of interest?	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Were participants analyzed in the groups to which they were randomized?	Were outcomes measured in the same way for treatment groups?	Were outcomes measured in a reliable way?	Was appropriate statistical analysis used?	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?
Lever et al., 1987	Yes	Yes	Yes	No	No	No	Yes	No, yes	Yes	Yes	Yes	Yes	No
Estlin et al., 2001	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Cheng et al., 2003	Yes	Yes	Yes	No	No	No	Yes	No, yes	Yes	Yes	Yes	Yes	No
Cheng et al., 2004	Yes	Yes	Yes	No	No	No	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Schmid et al., 2006	Yes	Yes	Yes	No	No	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Cruz et al., 2007	Yes	Yes	Yes	Unclear	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Cubukcu et al., 2007	Unclear	Yes	Yes	No	No	No	Yes	Unclear	Yes	Yes	Yes	No	Yes
de Koning et al., 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes

El-Housseiny et al., 2007	Yes	Yes	Yes	No	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Gandemer et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Sung et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Kuhn et al., 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes
Tomazevic et al., 2013	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Amadori et al., 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Bardellini et al., 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Bardellini et al., 2016 2	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Gholizadeh et al., 2016	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes
Hamidieh et al., 2016	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lucchese et al., 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medeiros-Filho et al., 2017	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes
Pourdeghatkar et al., 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Vitale et al., 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes

Bostanabad et al., 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Gobbo et al., 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Ribeiro da Silva et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Alkhouli et al., 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Immonen et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Kamsvåg et al,. 2020	Yes	Yes	Yes	No	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Mubaraki et al., 2020	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	No	Yes
Prakash et al., 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Alkhouli et al., 2021 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Alkhouli et al., 2021 3	Yes	Yes	Yes	Yes	No	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Fiwek et al., 2022	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Hassan et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes
Guimaraes d et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, no	Yes	Yes	Yes	Yes	Yes
Badr et al 2023	Yes	Yes	Yes	No	Yes	Yes	Yes	No, yes	Yes	Yes	Yes	Yes	Yes

Abdulrhmanm et al., 2012	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Al Jaouni et al., 2027	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 6. JBI Critical Appraisal Checklist of Case Reports.

Author(s) (year of publication)	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?
Rimulo, A. L. et al. 2011	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
Inati, A. et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
Lima Arrais Ribeiro, I. et al., 2015	Yes	Yes	Yes	No	No	No	Not applicable	Yes

Appendix 6. JBI Critical Appraisal Checklist of Cross-Sectional studies:

Author(s) (year of publication)	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
Ali, M. H. M. et al., 2019	No	Yes	Yes	Yes	No	No	Yes	No
Devi, K. S. et al., 2019	No	Yes	Yes	Yes	No	No	Yes	No
Kapoor, G. et ak., 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Lucena, N. N. N. et al., 2019	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Coelho, M. C. et al., 2022	Yes	Yes	Yes	Yes	Yes	No	Yes	No

Appendix 6. JBI Critical Appraisal Checklist of Case control studies:

Author(s) (year of publication)	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Were cases and controls matched appropriately?	Were the same criteria used for identification of cases and controls?	Was exposure measured in a standard, valid and reliable way?	Was exposure measured in the same way for cases and controls?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	Was the exposure period of interest long enough to be meaningful?	Was appropriate statistical analysis used?
Karolewska et al., 2008	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Bektaş-Kayhan et al., 2012	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Soto et al., 2015	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Pels et al., 2017	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Bezinelli et al., 2015	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Lauritano et al., 2013	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes

4. CONSIDERAÇÕES FINAIS

A MO é uma complicação comum em pacientes pediátricos submetidos a tratamentos oncológicos, como QT e RT-CP. A avaliação sistemática e precisa dessa condição é de extrema importância, uma vez que a MO pode não apenas causar significativo desconforto e dor nas crianças, mas também comprometer a alimentação adequada, levando a complicações adicionais. Escalas de MO que atendam às necessidades específicas da população pediátrica e sua padronização, estimulam a sua aceitação pela comunidade médica e a implementação consistente na prática clínica. Além disso, permite intervenções precoces para minimizar o impacto negativo nos pacientes pediátricos em tratamento contra o câncer, e facilita a comunicação entre profissionais de saúde, promovendo uma linguagem comum e compreensível no monitoramento da MO.

Adicionalmente, a importância das escalas de avaliação transcende o âmbito clínico, contribuindo para a pesquisa e o avanço científico. A padronização na mensuração da MO em crianças facilita a coleta de dados uniformes, permitindo a comparação entre estudos e a elaboração de diretrizes mais robustas no manejo dessa condição específica.

O presente trabalho revelou uma prevalência notável de estudos que empregaram a escala de MO da OMS, que tem como foco a avaliação específica das lesões orais. No entanto, um aspecto crucial é a falta de validação específica dessa escala para crianças, o que implica em limitações significativas ao aplicá-la nesse grupo populacional. A escala ChIMES é uma ferramenta promissora, desenvolvida considerando as particularidades da população infantil. A ChIMES proporciona o autorrelato do paciente, permitindo que as crianças expressem experiências subjetivas e sintomas de forma única, que podem não ser totalmente capturados pela observação clínica isolada. No entanto, por não possuir uma avaliação específica de lesões, nosso estudo recomenda a combinação do CHIMES com a escala da OMS, juntando características clínicas e subjetivas. Como complemento, escalas de dor e PROMs aumentam a precisão da avaliação.

REFERÊNCIAS

ABDALLA-ASLAN R, ZADIK Y, INTRATOR O, BARDELLINI E, CHENG KKF, BOSSI P, ET AL. Clinical use of photobiomodulation for the prevention and treatment of oral mucositis: the real-life experience of MASCC/ISOO members. ***Support Care Cancer,*** *v. 31, n. 8, p. 481, 2023.*

AGGARWAL R, BANSAL D, NARU J, SALARIA M, RANA A, MINZ RW, ET AL. HSV-1 as well as HSV-2 is frequent in oral mucosal lesions of children on chemotherapy. ***Support Care Cancer,*** *v. 22, n. 7, p. 1773-1779, 2014.*

ALHUSSAIN A, ALKHAYAL Z, AYAS M, ABED H. Prevalence and risk factors of oral mucositis in paediatric patients undergoing haematopoietic stem cell transplantation. ***Oral diseases,*** *v. 28, n. 3, p. 657-669, 2022.*

ANDERSON PM, SCHROEDER G, SKUBITZ KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. **Cancer,** v. 83, n. 7, p. 1433-9, 1998.

ANTUNES HS, HERCHENHORN D, SMALL IA, ARAÚJO CMM, VIÉGAS CMP, CABRAL E, ET AL. Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation, ***Radiotherapy & Oncology,*** *v.109, n. 2, p. 297–302, 2013.*

AQUINO VM, HARVEY AR, GARVIN JH, GODDER KT, NIEDER ML, ADAMS RH. A double-blind randomized placebo-controlled study of oral glutamine in the prevention of mucositis in children undergoing hematopoietic stem cell transplantation: a pediatric blood and marrow transplant consortium study. ***Bone Marrow Transplant.*** *v. 36, n. 7, 611–616, 2005*

ARIYAWARDANA A, CHENG KK, KANDWAL A, TILLY V, AL-AZRI AR, GALITI D, ET AL. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. ***Supportive Care in Cancer,*** *v. 27, n. 10, p. 3985-3995, 2019.*

ATTINA G, ROMANO A, MAURIZI P, D'AMURI S, MASTRANGELO S, CAPOZZA MA ET AL. Management of Oral Mucositis in Children With Malignant Solid Tumors. ***Frontiers in Oncology,*** *v. 11, n. 1, p. 1-7, 2021*

AVRITSCHER EB, COOKSLEY CD, ELTING LS. Scope and epidemiology of cancer therapy-induced oral and gastrointestinal mucositis. **Seminars in Oncology Nursing,** v. 20, n. 1, p. 3–10, 2004.

BELLM LA, CUNNINGHAM G, DURNELL L, EILERS J, EPSTEIN JB, FLEMING, T., ET AL. Defining clinically meaningful outcomes in the evaluation of new treatments for oral mucositis: Oral mucositis patient provider advisory board. **Cancer Investigation,** v. 20, n. 5-6, p. 793–800, 2002.

BELLM LA, EPSTEIN JB, ROSE-PED A, MARTIN P, FUCHS HJ. Patient reports of complications of bone marrow transplanta-tion. **Support Care Cancer,** v. 8, n. 1, p. 33–39, 2000.

BLIJHAM GH. Prevention and treatment of organ toxicity during high-dose chemotherapy: an overview. ***Anti-Cancer Drugs,*** *v. 4, n. 5, p. 527-533, 1993.*

BOCHUD PY, CALANDRA T, FRANCIOLI P. Bacteremia due to viridans streptococci in neutropenic patients: a review. ***The American Journal of Medicine, v.*** *97, n. 3, p. 256–264, 1994.*

BOCKEL S, VALLARD A, LEVY A, FRANCOIS S, BOURDIS M, LE GALLIC C, ET AL. Pharmacological modulation of radiation-induced oral mucosal complications. ***Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique,*** *v. 22, n. 5, p. 429-437, 2018.*

BONASSA, EMA. Terapêutica Oncológica para Enfermeiros e Farmacêuticos. São Paulo: Atheneu, 2023.

BONOMO P, ELAD S, KATAOKA T, BOSSI P. The impact of the COVID-19 outbreak on supportive care for oral mucositis: current concepts and practice. ***Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer,*** *v. 29, n. 5, p. 2255-2258, 2021.*

BROWN CG, WINGARD J. Clinical consequences of oral mucositis. ***Semin Oncol Nurs,*** *v. 20, n. 1, p. 16–21, 2004.*

BUCEKOVA M, JARDEKOVA L, JURICOVA V, BUGAROVA V, DI MARCO M, GISMONDI A, ET AL. Antibacterial Activity of Different Blossom Honeys: New Findings. ***Molecules (Basel, Switzerland),*** *v. 24, n. 8, p. 1573, 2019.*

BULUT HK, TUFEKCI FG. Honey prevents oral mocositis in children undergoing chemotherapy: A quasi-experimental study with a control group. ***Complementary Therapies in Medicine,*** *v. 29, n. 9, p. 132-140, 2016.*

CACCELLI EMN, PEREIRA MLM, RAPOPORT A. Avaliação da mucosite e xerostomia como complicações do tratamento de radioterapia no câncer de boca e orofaringe. ***Rev Bras Cir Cabeça e Pescoço,*** *v. 38, n. 2, p. 80-3, 2009*

Cancer. ***World Health Organisation, 2022.*** *Disponível em*: *https://www.who.int/health-topics/cancer#tab=tab_1 Acesso em 7 out. 2023*

CELLA D, PULLIAM J, FUCHS H, MILLER C, HURD D, WINGARD JR, ET AL. Evaluation of pain associated with oral mucositis during the acute period after administration of high-dose chemotherapy. **Cancer**, v. 98, n 2, p. 406–412, 2003.

CHILDERS NK, STINNETT EA, WHEELER P, WRIGHT JT, CASTLEBERRY RP, DASANAYAKE AP. Oral complications in children with cancer. ***Oral Surg Oral Med Oral Pathol,*** *v. 75, n. 1, p. 41-47 , 1993.*

CHENG KK, GOGGINS WB, LEE VW, THOMPSON DR. Risk factors for oral mucositis in children undergoing chemotherapy: a matched case–control study. ***Oral Oncology,*** *v. 44, n. 11 p. 1019–1025, 2008.*

CHEN CF, WANG RH, CHENG SN, CHANG YC. Assessment of chemotherapy induced oral complications in children with cancer. ***J. Pediatr. Oncol. Nurs, v.*** *21, n. 1, p. 33–39, 2004.*

CHENG KK, MOLASSIOTIS A, CHANG AM. An oral care protocol intervention to prevent chemotherapy-induced oral mucositis in paediatric cancer patients: a pilot study. ***European Journal of Oncology Nursing,*** *v. 6, n. 2, p. 66–73, 2002.*

CORREA MEP, CHENG KKF, CHIANG K, KANDWAL A, LOPRINZI CL, MORI T, ET AL. Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. ***Support Care Cancer,*** *v. 28, n. 5, p. 2449-2456, 2020.*

CURRA M, JUNIOR LA, MARTINS MD, SANTOS PS. Chemotherapy protocols and incidence of oral mucositis. An integrative review. ***Einstein (Sao Paulo, Brazil),*** *v. 16, n. 1, p. 1-9, 2018*

DE MARTEL C, GEORGERS D, BRAY F, FERLAY J, CLIFFORD GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. ***Lancet Glob Health,*** *v. 8, n. 2, p. 180-190, 2020.*

DEVI KS, ALLENIDEKANIAB A. The relationship of oral care practice at home with mucositis incidence in children with acute lymphoblastic leukemia. ***Comprehensive Child and Adolescent Nursing,*** *v. 42, n. 1, p. 56-64, 2019.*

DE ARRUDA JAA, HEIMLICH FV, DRUMOND VZ, SCHUCH LF, MARTINS MD, ABREU LG, ET AL. Association of anxiety and depression with oral mucositis: A systematic review. ***Oral diseases,*** *v. 29, n. 7, p. 2538-2551, 2023.*

DODD MJ, MIASHOWSKI C, DIBBLE SL, PAUL SM, MACPHAIL L, GREENSPAN D, ET AL. Factors influencing oral mucositis in patients receiving chemotherapy. ***Cancer Practice,*** *v. 8, n. 6, p. 291–297, 2000.*

DRULEY TE, HAYASHI R, MANSUR DB, ZHANG QJ, BARNES Y, TRINKAUS K, ET AL. Early outcomes after allogeneic hematopoietic SCT in pediatric patients with hematologic malignancies following single fraction TBI. ***Bone Marrow Transplant,*** *vol 43, n. 3, p. 307–314, 2009.*

ECOG Performance Status Scale. ***Eastern Cooperative Oncology Group (ECOG),*** *2022. Disponível em: https://ecog-acrin.org/resources/ecog-performance-status. Acesso em Acesso em 4 out. 2023.*

EISER C, MORSE R. Can parents rate their child's health-related quality of life? Results of a systematic review. ***Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation,*** *v. 10, n. 4, p. 347-57, 2001.*

ELAD S, CHENG KKF, LALLA RV, YAROM N, HONG C, LOGAN RM, BOWEN J, GIBSON R, ET AL. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. ***Cancer,*** *v. 126, n. 19, p. 4423–4431, 2020.*

ELAD S, YAROM N, ZADIK Y, KUTEN-SHORRER M, SONIS ST. The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies. ***CA: a cancer journal for clinicians,*** *v. 72, n. 1, p. 57-77, 2022*

ELHADAD MA, EL-NEGOUMY E, TAALAB MR, IBRAHIM R, ELSAKA RO. The effect of topical chamomile in the prevention of chemotherapy-induced oral mucositis: A randomized clinical trial. **Oral diseases,** v. 28, n. 1, p. 164-172, 2022.

ETHIER MC, REGIER DA, TOMLINSON D, JUDD P, DOYLE J, GASSAS A, ET AL. Perspectives toward oral mucositis prevention from parents and health care professionals in pediatric cancer. ***Support Care Cancer,*** *v, 20, n. 8, p 1771-1777, 2012.*

FIGLIOLIA SL, OLIVEIRA DT, PEREIRA MC, LAURIS JRP, MAURICIO AR, DE ANDREA MLM. Oral mucositis in acute lymphoblastic leukaemia: analysis of 169 paediatric patients. Oral Diseases, v. 14, n. 8, p. 761–766, 2008.

FRANCO P, MARTINI S., DI MUZIO, J., CAVALLIN, C., ARCADIPANE, F., RAMPINO, M., OSTELLINO, O., PECORARI, G., GARZINO DEMO, P., FASOLIS, M., AIROLDI, M., RICARDI, U.. Prospective assessment of oral mucositis and its impact on quality of life and patient-reported outcomes during radiotherapy for head and neck cancer. ***Medical oncology (Northwood, London, England),*** *v. 34, n. 5, p. 81, 2017.*

FREITES-MARTINES A, SANTANA N, ARIASP-SANTIAGO S, VIERA A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. **Actas dermo-sifiliograficas,** v. 112, n. 1, p. 90-92, 2021.

GABRIEL AF, SILVEIRA FM, CURRA M, SCHUCH LF, WAGNER VP, MARTINS MAT, MATTE US, ET ALl. Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis. ***Oral diseases,*** *v. 28, n. 4, p. 1068-1084, 2022*

GONZALEZ-ARRIGADA WA, OTTAVIANI G, DEAN D, SANTOS-SILVA AR, TREISTER NS. Editorial: Oral complications in cancer patients. ***Frontiers in oral health,*** *v. 3, n. 1, p. 1-3, 2022.*

GUTIERREZ-VARGAS R, DIAZ-GARCIA ML, VILASSIS-KEEVER MA, PORTILLA-ROBERTSON J, ZAPATA-TARRES M. Instruments to measure the quality of life in patients with oral mucositis undergoing oncological treatment: a systematic review of the literature. ***Boletin medico del Hospital Infantil de Mexico,*** *v. 73, n. 6, p. 457–466, 2016*

HAWKINS D, HOURELD N, ABRAHAMSE H. Low level laser therapy (LLLT) as an effective therapeutic modality for delayed wound healing. Annals of New York Acadadeny of Sciences, v. 1056, n. 1 p. 486-93, 2005.

HOUGHTON PJ, KURMASHEVA RT. Challenges and Opportunities for Childhood Cancer Drug Development. Pharmacological reviews, v. 71, n. 4, p. 671–697, 2019.

HURREL L, BURGOYNE L, LOGAN RM REVESZ T. The Management of Pediatric Oncology Inpatients With Oral Mucositis. ***Journal of pediatric hematology/oncology,*** *v. 41, n. 8, p. 510-516, 2019.*

Instituto Nacional de Câncer - INCA. Câncer infantojuvenil. ***Ministério da saúde,*** *2022. Disponível em: https://www.gov.br/inca/pt-br/assuntos/cancer/tipos/infantojuvenil . Acesso em 4 out. 2023.*

JACOBS S, BAGGOTT C, AGARWAL R, HESSER T, SCHECHTER T, JUDD P, ET AL. Validation of the Children's International Mucositis Evaluation Scale (ChIMES) in paediatric cancer and SCT. ***British Journal of Cancer****, v. 109, n. 10, p. 2515-2522, 2013.*

JARONESKI LA. The importance of assessment rating scales for chemotherapy-induced oral mucositis. ***Oncology Nursing Forum,*** *v. 33, n. 6, p. 1085-1093, 2006.*

KAMRANI A, HOSSEINZADEH R, SHOMALI N, HERIS JA SHAHABI P, MOHAMMADINASAB R, ET AL. New immunotherapeutic approaches for cancer treatment. ***Pathology, research and practice****, v. 248, n. 1****,*** *p. 154-632, 2023.*

KAUARK-FONTES, E., MIGLIORATI CA, EPSTEIN JB, BENSADOUN R, GUEIROS LA, CARROLL J, ET AL. Twenty-year analysis of photobiomodulation clinical studies for oral mucositis: a scoping review. ***Oral surgery, oral medicine, oral pathology and oral radiology,*** *v. 135, n. 5, p. 626-641, 2023.*

KAUARK-FONTES E, MIGLIORARI CA, EPSTEIN JB, TREISTER NS, ALVES CGB, FARIA KM, ET AL. Extraoral photobiomodulation for prevention of oral and oropharyngeal mucositis in head and neck cancer patients: interim analysis of a randomized, double-blind, clinical trial. ***Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer,*** *v. 30, n. 3, p. 2225-2236, 2022.*

KAUARK-FONTES E, RODRIGUES-OLIVEIRA L, EPSTEIN JB, FARIA KM, ARAUJO ALD, GUEIROS LAM, ET AL. Cost-efectiveness of photobiomodulation therapy for the prevention and management of cancer treatment toxicities: a systematic review. ***Support Care Cancer,*** *v. 29, n. 6, p. 2875–2884, 2021.*

KAMSVAG-MAGNUSSON T, THORSELL CEDERBERG J, SVANBERG A, VON ESSEN L, ARVIDSON J, MELLGREN K, ET AL. Parents and children's perceptions of distress related to oral mucositis during haematopoietic stem cell transplantation. Acta paediatrica, v. 103, n. 6, p. 630-636, 2014.

KENNEDY L, DIAMOND J. Assessment and management of chemotherapy-induced mucositis in children. ***J Pediatr Oncol Nurs, v.*** *14, n. 3, p. 164–174, 1997.*

KHAW A, LIBERAL S, LOGAN R, KEEFE D, BERTOLD M. Influence of periodontitis on the experience of oral mucositis in cáncer patients undergoing head and neck radiotherapy: a pilot study. ***Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer,*** *v. 22, n. 8, p. 2119-25, 2014.*

LALLA RV, BRENNAN MT, GORDON SM, SONIS ST, ROSENTHAL DI, KEEFE DM. Oral mucositis due to high-dose chemotherapy and/or head and neck radiation therapy. Journal of the National Cancer Institute. Monographs, v. 2019, n. 53, p. 17-24, 2019.

LINDER LA, HOOKE MC. Symptoms in Children Receiving Treatment for Cancer-Part II: Pain, Sadness, and Symptom Clusters. ***Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses,*** *v. 36, n. 4, p. 262-279, 2019.*

LIU TM, LUO YW, TAM KW, LIN CC, HUANG TW. Prophylactic and therapeutic effects of honey on radiochemotherapy-induced mucositis: a meta-analysis of randomized controlled trials. ***Support Care Cancer, v. 27, n. 7, p.*** *2361-2370, 2019.*

MCGUIRE DB. Barriers and strategies in implementation of oral care standards for cancer patients. ***Supportive Care in Cancer,*** *v. 11, n. 7, p. 435–441, 2003.*

MENDONÇA RM, ARAUJO M, LEVY CE, MORARI J, SILVA RA, YUNES JA, BRANDALISE, SA. Oral mucositis in pediatric acute lymphoblastic leukemia patients: evaluation of microbiological and hematological factors. ***Pediatr Hematol Oncol, v. 32, n. 5, p. 322-30, 2015.***

MORAIS EF, LIRA JAS, MACEDO RAP, SANTOS KS, ELIAS CTV, MORAIS, MLSA. Oral manifestations resulting from chemotherapy in children with acute lymphoblastic leukemia. ***Brazilian Journal of Otorhinolaryngology,*** *v. 80, n. 1, p. 78–85, 2014.*

MORAIS-FARIA K, PALMIER NR, CORREIA JL, JUNIOR GC, DIAS RB, PINTO HG, ET AL. Young head and neck cancer patients are at increased risk of developing oral mucositis and

trismus. ***Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer,*** *v. 28, n. 9, p. 4345-4352, 2020.*

OOSTEROM N, DIRKS NF, HEIL SG, DE JONGE R, TISSING WJE, PIETERS R, ET AL. A decrease in vitamin D levels is associated with methotrexate-induced oral mucositis in children with acute lymphoblastic leukemia. ***Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer,*** *v. 27, n. 1, p. 183-190, 2019.*

Oral Complications of Chemotherapy and Head/Neck Radiation (PDQ®)–Patient Version. National Cancer Institute, 2023. Disponível em https://www.cancer.gov/about-cancer/treatment/side-effects/mouth-throat/oral-complications-pdq. Acesso em 7 out. 2023

OTMANI N, HATTAD S. Clinical Outcome in Children with Chemotherapy-Induced Mucositis. ***Seminars in oncology nursing,*** *v. 37, n. 3, p. 151-160, 2021.*

PAIVA BSR, BARROSO EM, CADAMURO SA, DE PAULA LAB, PIROLA WE, SERRANO CVMP, PAIVA CE. The Children's International Mucositis Evaluation Scale Is Valid and Reliable for the Assessment of Mucositis Among Brazilian Children With Cancer. ***J Pain Symptom Manage,*** *v. 56, n. 5, p. 774-780, 2018.*

PALMER MK. WHO Handbook for Reporting Results of Cancer Treatment. ***British Journal of Cancer,*** *v. 45, n.3, p. 484–485, 1982.*

QUTOB AF, ALLEN G, GUE S, REVESZ T, LOGAN RM KEEFE D. Implementation of a hospital oral care protocol and recording of oral mucositis in children receiving cancer treatment : a retrospective and a prospective study. **Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer,** v. 21, n. 4, p. 1113-20, 2013.

REYAD FA, ELSAYED NM, CHAZLI YE. Photobiomodulation for chemotherapy-induced oral mucositis in leukemic children: A randomized controlled clinical trial. ***Oral diseases,*** *v. 29, n. 5, p. 2239-2247, 2023.*

RODRIGUES-OLIVEIRA L, KOWALSKI LP, SANTOS M, MARTA GN, BENSADOUN R, MARTINS MD ET AL. Direct costs associated with the management of mucositis: A systematic review. ***Oral oncology,*** *v. 118, n. 1, p. 1-16, 2021.*

SCULLY C, EPSTEIN J, SONIS ST. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy. Part 2: diagnosis and management of mucositis. ***Head & neck,*** *vol. 26, n. 1, p. 77-84, 2004.*

SCULLY C, SONIS S, DIZ PD. Oral mucositis. ***Oral Diseases,*** *v. 12, n. 3, p. 229–241, 2006.*

SEZGIN MG, BEKTAS H, OZER Z. The effect of cryotherapy on oral mucositis management in patients undergoing stem cell transplantation: A systematic review of randomized controlled trials. ***International Journal of Nursing Practice,*** *v. 29, n. 4, p. 13102, 2023.*

SOARES AF, ANQUINO ARL, CARVALHO CHP, NONAKA CFW, ALMEIDA D, PINTO LP. Frequency of oral mucositis and microbiological analysis in children with acute lymphoblastic leukemia treated with 0.12% chlorhexidine gluconate. ***Brazilian dental journal,*** *v. 22, n. 4, p. 312–6, 2011.*

SONIS ST, HASHEMI S, EPSTEIN JB, NAIR RG, RABER-DURLACHER JE. Could the biological robustness of low level laser therapy (Photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. ***Oral Oncol,*** *v 54, n. 1, p. 7-14, 2016*

SONIS ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. ***Oral Oncology,*** *v. 45, n. 12, p. 1015–1020, 2009.*

SONIS ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. ***Oral oncology,*** *v. 34, n. 1, p. 39-43, 1998.*

SONIS ST. Oral Mucositis. ***Anti-Cancer Drugs,*** *v. 22, n. 7, p. 607–612, 2011.*

SONIS ST, OSTER G, FUCHS H, BELLM L, BRADFORD WZ, EDELSBER J, ET AL. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. ***Journal of Clinical Oncology,*** *v. 19, n. 8, p. 2201–2205, 2001.*

SONIS ST. Oral mucositis in head and neck cancer: risk, biology, and management. ***American Society of Clinical Oncology Educational Book,*** *v. 33, n. 33, p. 236-240, 2013.*

SONIS ST. The pathobiology of mucositis. ***Nature reviews. Cancer,*** *v. 4, n. 4, p. 277-84, 2004.*

SURESH AVS, VARMA PP, SINHA S, DEEPIKA S, RAMAM R, SRINIVASAN M, ET AL. Risk-scoring system for predicting mucositis in patients of head and neck cancer receiving concurrent chemo radio- therapy. ***Journal of Cancer Research and Therapeutics,*** *v.6, n 4, p. 448-451, 2010.*

SUNG L, TOMLINSON GA, GREENBERG ML, KOREN G, JUDD P, OTA S, FELDMAN BM. Validation of the oral mucositis assessment scale in pediatric cancer. ***Pediatric Blood & Cancer.*** *v. 49, n. 2, p. 149-153, 2007.*

TREISTER N, NIEDER M, BAGGOTT C, OLSON E, CHEN L, DANG H, ET AL. Caphosol for prevention of oral mucositis in pediatric myeloablative haematopoietic cell transplantation. ***British journal of cancer,*** *v. 116, n. 1, p. 21-27, 2017.*

TROTTI A, BELLM LA, EPSTEIN JB, FRAME D, FUCHS HJ, GWEDE CK, ET AL. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. ***Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology,*** *v. 66, n. 3, p. 253-62, 2003*

TOMLINSON D, DUPUIS LLD, GIBSON P, JOHNSTON DL, PORTWINE C, BAGGOTT C, ET AL. Initial development of the Symptom Screening in Pediatrics Tool (SSPedi). ***Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer,*** *v. 22, n. 1, p. 71-75, 2014*

TOMLINSON D, ISITT JJ, BARRON RL, DOYLE J, JUDD P, GASSAS A, ET AL. "Determining the understandability and acceptability of an oral mucositis daily questionnaire. ***Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses,*** *v. 25, n. 2, p. 107-11, 2008.*

TOMLINSON D, GIBSON F, TREISTER N, BAGGOT C, JUDD P, HENDERSHOT E, ET AL. Refinement of the Children's International Mucositis Evaluation Scale (ChIMES): child and parent perspectives on understandability, content validity and acceptability. ***European journal of oncology nursing : the official journal of European Oncology Nursing Society,*** *v. 14, n. 1, p. 29-41, 2010.*

TOMLINSON D, GIBSON F, TREISTER N, BAGGOTT C, JUDD P, HENDERSHOT E, ET AL. Challenges of mucositis assessment in children: expert opinion. ***European journal of oncology nursing : the official journal of European Oncology Nursing Society,*** *v. 12, n. 5, p. 469-75, 2008.*

TOMLINSON D, GIBSON F, TREISTER N, et al. Designing an oral mucositis assessment instrument for use in children: generating items using a nominal group technique. ***Support Care Cancer, v.*** *17, n. 5, p. 555-562, 2009.*

TOMLISNON D, GIBSON F, TREISTER N, et al. Understandability, content validity, and overall acceptability of the Children's International Mucositis Evaluation Scale (ChIMES): child and parent reporting. ***Journal of pediatric hematology/oncology,*** *v. 31, n. 6, p. 416-423. 2009.*

TOMLINSON D, JUDD P, HENDERSHOT E, MALONEY AM, SUNG L. Establishing literature-based items for an oral mucositis assessment tool in children. ***Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses,*** *v. 25, n. 3, p. 139-147, 2008.*

TOMLINSON D, JUDD P, HENDERSHOT E, MALONEY AM, SUNG L. Measurement of oral mucositis in children: a review of the literature. ***Support Care Cancer,*** *v. 15, n. 11, p. 1251-1258, 2007.*

VAGLIANO L, FERAUT C, GOBETTO G, TRUNFIO A, ERRICO A, CAMPANI V. Incidence and severity of oral mucositis in patients undergoing haematopoietic SCT–results of a multicentre study. ***Bone Marrow Transplant, v.*** *46, n. 5, p. 727–732, 2011.*

VILLA A, SONIS ST. An update on pharmacotherapies in active development for the management of cancer regimen-associated oral mucositis. ***Expert Opinion on Pharmacotherapy,*** *v. 21, n. 5, p. 541–548, 2020.*

VILLA A, SONIS ST. Mucositis: pathobiology and management. ***Current Opinion in Oncology,*** *v. 27, n. 3, p. 159–164, 2015*

WARD LM, COOPER SA, HUGHES-MCCORMACK L, MACPHERSON L, KINNEAR D. Oral health of adults with intellectual disabilities: a systematic review. ***J Intellect Disabil Res.*** *v. 63, n. 1. p. 1359-1378, 2019.*

World Health Organisation. International Agency for Research on Cancer. Global Cancer Observatory, 2022. Disponível em https://gco.iarc.fr/tomorrow/en/dataviz/isotype?age_end=0&single_unit=10000&years=2040&types=0. Acesso em 4 out. 2023.

YAVUZ, B.; BAL Y LMAZ, H. Investigation of the Effects of Planned Mouth Care Education on the Degree of Oral Mucositis in Pediatric Oncology Patients. Journal of Pediatric Oncology Nursing, v. 32, n. 1, p. 47–56, 2014.

YAVUZ B, YILMAZ HB. Investigation of the effects of planned mouth care education on the degree of oral mucositis in pediatric oncology patients. ***Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses,*** *v. 32, n. 1, p. 47-56, 2015.*

YEH CH, CHANG CW, CHANG PC. Evaluating quality of life in children with cancer using children's self-reports and parent-proxy reports. ***Nurs. Res****, v. 54, n. 5, p. 354–362, 2005.*

ZADIK Y, ARANY PR, FREGNANI ER, BOSSI P, ANTUNES HS, BENSADOUN R, ET AL. Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. ***Support Care Cancer,*** *v. 27, n. 10, p. 3969-3983, 2019.*

ZHANG L, XING D, GAO X, WU S. Low-power laser irradiation promotes cell proliferation by activating PI3K/Akt pathway. ***Journal of Celluar Physiology,*** *v. 219, n. 3,* ***p.*** *553-562, 2009.*

ANEXO 1- Registro do protocolo de revisão sistemática na base PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Clinical assessment of oral mucositis in pediatric patients: a systematic review

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation

Manoela Martins, Júlia Soares, Laura Kirschnick, Amanda Gabriel, Lauren Schuch, Felipe Silveira, Alan Santos-Silva. Clinical assessment of oral mucositis in pediatric patients: a systematic review. PROSPERO 2022 CRD42022333966 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022333966

Review question

How has oral mucositis and its adverse effects been evaluated and classified in oncologic pediatric patients?

Searches

The search strategy was constructed according to the Populations, Exposure, Comparison, Outcomes and Study Design (PECOS) principle. Individual search strategies were designed for the following electronic databases: MEDLINE/PubMed, EMBASE, Web of Science and Scopus. The searched publications were only considered in the English language, with no restrictions on year of publication. The search strategy contained a combination of controlled predefined Medical Subject Heading (MeSH) terms and free terms using the Boolean operators (i.e., OR, AND), always adapted to the rules of syntax of each bibliographic database. The following search strategy was constructed: (Stomatitis OR Stomatitides OR "Oral Mucositis" OR "Mucositides, Oral" OR "Oral Mucositides" OR Oromucositis OR Oromucositides OR "Mucositis, Oral") AND (Child OR Children OR Pediatric OR Pediatrics OR Paediatric OR Infant) AND ("Patient Reported Outcome Measures" OR "Patient Reported Outcome Measure" OR "Patient Reported Outcomes" OR "Outcome, Patient Reported" OR "Patient Reported Outcome" OR "Patient-Reported Outcome" OR "Outcome, Patient-Reported" OR "Patient-Reported Outcomes" OR Assessment OR "Oral Mucositis Assessment Scale" OR "Instrument Development" OR "Measurement of Oral Mucositis" OR Evaluation Scales of Oral Mucositis"). Additionally, it was also performed a manual search of bibliographies and reference lists of the included studies to locate any potential unidentified study.

Types of study to be included

Observational studies.

Condition or domain being studied

Tomlinson et al. 2007 made a review in all the oral mucositis evaluation scales created, with a didactic division between simple, objective and objective/subjective/functional. Despite these scales were designed for adults, three of them were used to evaluate oral mucositis in pediatric oncology patients – oral assessment guide, oral mucositis assessment scale and The Walsh Scale. The use of an adult instrument in pediatric patients has known challenges as ensure the optical visualization, children's cooperation and their ability to report subjective and functional characteristics. In 2013, the same group, developed a new scale, designed directly for children patients: electronic Children's International Mucositis Evaluation Scale. Despite the recognized use of these four instruments to evaluate oral mucositis in pediatric patients, the literature doesn't yet have a consensus on the best and most didactic instrument to evaluate oral mucositis in children and its adverse effects. In this scenario, this systematic review aims to raise all the scales used in pediatric patients and reported in the literature, their individual characteristics and in the end, propose the justified use of the most complete

and didactic instrument.

Participants/population

Pediatric patients undergoing oncological treatment

Intervention(s), exposure(s)

Exposure: oral mucositis.

Comparator(s)/control

None or baseline assessment.

Main outcome(s)

Identify the reported evaluation scales for oral mucositis used in pediatric oncology patients and their individual characteristics.

Measures of effect

Relative risk, Odds ratio.

Additional outcome(s)

Propose the most complete and didactic evaluation scale for children oncology patients.

Measures of effect

Not applicable.

Data extraction (selection and coding)

Titles and abstracts of all studies will be reviewed by two authors. If the title and abstract met with the eligibility criteria, the study will be included. Possible disagreements between the two authors will be solved by a third one. The reviewers will extract the following information from the selected studies: (1) publication details (first author and year); (2) population sample; (3) population age; (4) population sex; (5) study design; (6) evaluation scale used; (7) clinical characteristics of the patients; (8) additional comments on the scale; (9) main outcomes of the study.

Risk of bias (quality) assessment

Critical appraisal of the included articles was carried out by means of the Joanna Briggs Institute – University of Adelaide tool for case reports or case series. The included articles were evaluated according to the following parameters: clear description of patient's demographic characteristics, medical history and current clinical condition, clear description of the propaedeutic data, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report answered as "yes", "unclear", "no", or "not applicable". Risk of bias across studies was evaluated comparing sample characteristics variability, methodological heterogeneity, and risk of bias in individual studies. These judgements will be made independently by two review authors based on the criteria for judging the risk of bias. Disagreements will be resolved first by discussion and then by consulting a third author for arbitration.

Strategy for data synthesis

All results will be interpreted according to the information that was extracted from the studies. The level of consistency of the studies will depend on the extracted data. Common extracted data found in the studies will be categorized in groups for further comparison and analysis. Specific data from each study will be also tabulated and considered for

further separate description and discussion, whether it is relevant for the aim of our study and, consequently, the topic that is being assessed.

Analysis of subgroups or subsets

Not applicable.

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None.

Conflicts of interest

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Child; Humans; Neoplasms; Stomatitis

Date of registration in PROSPERO

30 May 2022

Date of first submission

19 May 2022

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

30 May 2022

30 May 2022