How to Cite:
Elgasmi, F. E., Al Jalil, Z., Elarabi, S., & Bensouda, S. (2022). Oral manifestations in children undergoing cancer therapy: An umbrella review. *International Journal of Health Sciences*, *6*(S1), 14074–14105. https://doi.org/10.53730/ijhs.v6nS1.8574

Oral manifestations in children undergoing cancer therapy: An umbrella review

Fatima Ezzahra Elgasmi
Department of Pediatric Dentistry, Faculty of Dental Medicine, Hassan II University, Casablanca, 21100 Morocco
Corresponding author email: shalu@smartgenpub.com

Zineb Al Jalil
Department of Pediatric Dentistry and Laboratory of Community Health, Epidemiology and Bio-statistics, Faculty of Dental Medicine, University Hassan, Hassan II University, Casablanca, 21100 Morocco

Samira Elarabi
Department of Pediatric Dentistry, Faculty of Dental Medicine, Hassan II University, Casablanca, 21100 Morocco

Sanaa Bensouda
Department of Pediatric Dentistry, Faculty of Dental Medicine, Hassan II University, Casablanca, 21100 Morocco

***Abstract*---**Introduction: According to data from the World Health Organization (WHO), cancer is diagnosed each year in about 300,000 children aged 0-19 years, with 1,000 new cases recorded each year in Morocco, in the population under 15 years of age. Anticancer therapies (chemotherapy, radiotherapy, surgery, biphosphonates ...) are often accompanied by various side effects sometimes disabling, those oral are very variable. The main manifestations described are: mucitis, xerostomia, infections, bleeding complications, caries, periodontal disease and dental anomalies, loss of taste, temporomandibular ankylosis, odontoradionecrosis, osteoradionecrosis, or radionecrosis related to biphosphonate use. In the literature, several studies focus on the relationship between childhood cancer, its treatment and its effect on the oral cavity. However, with the changes in protocols for the management of children with cancer, several studies have shown that advances in cancer therapy have had an impact on previously recognized oral complications. Aim: To analyze previously published systematic reviews on the oral manifestations of antimitotic therapy in children with a specific focus on their prevalence, prevention and management, in addition to highlighting the level of evidence from these reviews. Materials and methods: This study is an umbrella review that followed

Manuscript submitted: 18 March 2022, Manuscript revised: 9 April 2022, Accepted for publication: 27 May 2022

the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, developed with the systematic review guide. The bibliographic search was purely computer-based and was based on the interrogation of 5 databases: PUB MED / SCIENCE DIRECT / GOOGLE SCHOLAR / COCHRANE and CINAHL. It was spread over a period from March 2021 to June 2021. Results: Electronic searches retrieved a total of 7695 titles through searches of the following databases: The Pubmed search, via established Boolean equations, identified 33 articles. The Cochrane Library query yielded 25 articles. The query on Google scholar, resulted in a total of 5695 articles after applying filters. On Science direct, the search identified 623 articles. On CINAHL, 1319 articles were obtained. After title/abstract assessment and removal of duplicates,52 potentially eligible full-text articles were selected. Full-text reading excluded 22 articles, resulting in 30 systematic reviews that met the inclusion criteria. Inter-examiner reliability during full-text selection was recorded as high (kappa score 1.000). The article selection steps are shown in a flow chart, suggested by "The PRISMA 2020 Statement."Only one included systematic review fully met the AMSTAR 2 criteria. A total of nine were of low quality and 20 were rated as critically low quality. Discussion: Our Umbrella review has several strengths: - It provides an overview of available published systematic reviews of oral events related to cancer therapy in children using a transparent methodology. - It allows following the evolution of the knowledge concerning the manifestations in time because of the change of the antimitotic protocols. -It allows us to follow the evolution of the different preventive and therapeutic interventions that have or have not proven their worth in the field of oral complications of antineoplastic therapies in children. However, it is essential to note certain weaknesses that are not essentially related to the methodology of the umbrella review but rather to the lack of scientific evidence in the conclusions we were able to draw from the included systematic reviews (low to very low methodological quality according to AMSTAR 2). Conclusion: Through our review, we were able to highlight several spin-offs in the field of research and in the clinic which could be useful to us in order to bring out recommendations in the prevention and management of these oral complications as well as to conceive possibly anodontological guide of prevention and management of these complications, aimed at the pediatric population undergoing antimitotic therapy.

***Keywords*---**children, cancer therapy, bleeding complications.

Introduction

Anticancer therapies (chemotherapy, radiotherapy, targeted therapy, hematopoietic cell transplantation...) allow a possible total cure of the cancer, but unfortunately, they are often accompanied by various side effects that can be disabling. The oral and dental effects are very variable from one treatment to

another and from one child to another, due to the presence of organs in growth [1]. The main manifestations described are: mucositis, xerostomia, infections, bleeding complications, caries, periodontal disease and dental anomalies, loss of taste, temporomandibular ankylosis, osteoradionecrosis, or radionecrosis related to biphosphonates.

These complications vary essentially according to the type of cancer, the age of the patient, the type of antimitotic therapy and doses, the pre-existing oral condition and the level of oral care during treatment. Oral complications add to the various other manifestations experienced by the child with cancer and will further impair the child's quality of life. Mucositis is considered to be one of the most painful complications experienced by children in oncology and can also be a source of secondary infection, sometimes fatal in children with cancer. Antimitotic therapies can have an effect on blood cells, and thus lead to the occurrence of infection.

In the literature, several researches focus on the relationship between childhood cancer, its treatment and its effect on the oral cavity. Some authors show that children usually receive chemotherapy in cycles and that acute oral complications occur 5 to 7 days after the beginning of each cycle, corresponding to the decrease in leukocyte count. [2] Others emphasize that the incidence and severity of oral complications are associated with pre-existing factors (caries, gum disease, and poor hygiene) that clearly affect their emergence, increase, and persistence. In addition, children who have received cancer therapy may also develop dental and craniofacial problems that manifest at a later age.

However, with the changes in protocols in the management of the child with cancer, several studies have demonstrated that advances in cancer therapy have impacted previously recognized oral complications. [3] Indeed, several articles have focused on pharmacological and non-pharmacological approaches to prevent and treat certain oral complications such as mucositis.

The use of oral care protocols for prophylaxis such as cryotherapy, the use of growth factors (palifermin...), anti-inflammatory oral rinses (benzydamine...)... and the use of low-energy lasers has proven to be effective in the prevention and treatment of radiation-induced or chemically-induced mucositis, significantly reducing pain, severity and duration of ulceration and promoting healing of lesions. [4]

During the last decade, several systematic reviews have been published on the oral manifestations of anticancer therapies in children, thus allowing, at present, the availability of scientific data on this subject. This motivated us to carry out an umbrella review, whose objective was to analyze previously published systematic reviews on oral manifestations of antimitotic therapies in children, focusing specifically on prevalence, prevention, and management, and highlighting the level of evidence of these reviews.

Materials and Methods

The present study is an umbrella review that was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5], developed with the systematic review guide [6]. And in order to reduce unplanned duplication of the same topic, and in accordance with the PRISMA 2009 statement, a registration on the Prospero platform was performed**.** The study protocol being made publicly available under the registration number CRD42021284494.

1. Eligibility Criteria Used:

1.1. Inclusion criteria:

Any article defined as a systematic review meeting PRISMA criteria, any systematic review including children from birth to 16 years of age, any systematic review describing an oral complication related to one of the cancer therapies, and any article written in English were included.

PECO
P: Children undergoing and/or having undergone cancer therapy
E: Prevalence, prevention, management of oral manifestations
C: ----
O: Protocols for prevention and management of oral manifestations

1.2 Exclusion Criteria:

Excluded from this study was any article for which the full text was inaccessible for which we contacted the authors by email but we did not hear back from them.

2. Identification of the literature:

For study identification, our electronic search was based on querying five databases: PUB MED, COCHRANE, GOOGLE SCHOLAR, SCIENCE DIRECT, CINAHL. To make the best use of the available search engines, the search question must be clearly formulated. We used keywords, chosen according to the "Medical Subject Headings" (MeSH). Thus, the Boolean equation used for our search was: "Child OR Children AND Oncology AND Oral complications OR Oral manifestations OR Periodontal disease OR Oral mucositis OR Trismus OR Xerostomia". The duration of this computerized search was 4 months; from February 2021 to June 2021.

3. Selection of studies

3 authors (EF, BS and AZ) independently screened titles and abstracts. Inter-author agreement was assessed using the Kappa statistical test. Any paper classified as potentially eligible by one of the authors was ordered as full text and reviewed independently by the authors. Any disagreement was resolved through a three-way discussion.

4. Data extraction

The synthesis was done by a single author (EF) and first described the data of the included studies (author, year, type and number of included studies, number of participants, population, exposure, qualitative assessment tool, method of analysis, comparison, results, impact). Any disagreement was resolved through a three-way discussion.

5. Risk of bias assessment

The critical reading grid was completed by two examiners (EF and AZ), then the qualitative evaluation was done by three (EF, BS and AZ), according to the response to the 7 items considered critical areas in the AMSTAR 2, which consists of 16 items, which consist of a question and additional instructions for answer choices formulated as follows: ("yes", "partial yes" and "no") [7]. Agreement between reviewers was assessed by the Kappa test. Thus, the quality of systematic reviews was classified according to AMSTAR 2, into 4 categories: High: no weaknesses in critical areas or only one non-critical weakness, moderate: more than one non-critical weakness, low: one weakness in critical areas, with or without non-critical weaknesses, very low: more than one critical weakness, with or without non-critical weaknesses.

Results

1. Identification of the articles

Electronic searches retrieved a total of 7695 titles through database searches. Reading these titles resulted in a total of 68 articles being retained. After reading the abstracts of the 68 selected articles, 16 were eliminated. And after title/abstract evaluation and removal of duplicates, full-text reading excluded 22 articles, resulting in 30 systematic reviews that met the inclusion criteria. Inter-rater reliability during full-text selection was recorded as high (kappa score 1.000). The article selection steps are shown in a flow chart, suggested by "The PRISMA 2020 Statement" [8]. (Figure 1)

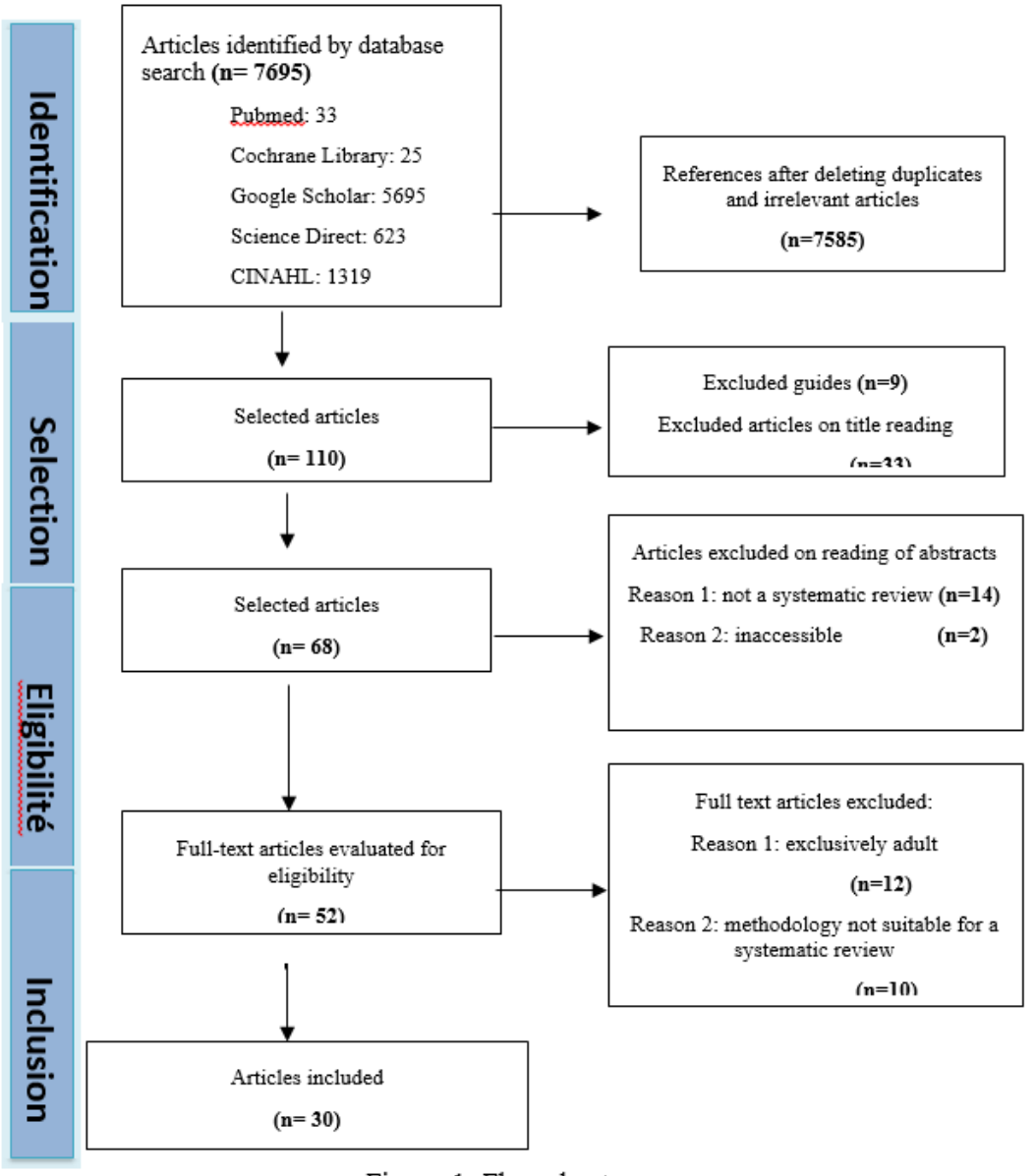

Figure 1: Flow chart

2. Characteristics of the included systematic reviews (Table I and II)

A total of 30 systematic reviews were included in this Umbrella review.
All systematic reviews covered a defined period.
Regarding language restriction, three systematic reviews did not report this feature [9,10,11], twenty-one had a language restriction [12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28, 29,30,31,32], six had no language restriction [33,34,35,36,37,38], and the non-English studies were translated.

Several subtopics in the systematic reviews were addressed.
For example: prevalence/incidence [12,14,17,21,22,23,24,27,33,38], description [9,11,12,13,15,21,22,24,26,32,38], prevention [10,14,16,18,20,21,22,24,26,28,29,30,31,33,35,37], and management [10,14,19,21,22,26,27,28,29,32,34, 35].

Table I: Bibliometric characteristics of the included systematic reviews

Authors	Year of publication	Types and numbers of studies included	Qualitative evaluation tools	Method of analysis	Studied variables
1. Worthington et al.	2002	24 randomizedstudies	Based on three criteria: concealment of randomization, double-blinding, and description of withdrawals and dropouts.	SR and MA	Oral Mucositis Oral candidiasis
2. .Napeñas et al.	2007	13 prospective clinical trials	Not cited	RS	Microorganisms isolated during chemotherapy
3. Tomlinson et al.	2008	21 original studies	Not cited	RS	Assessment tools for pediatric oral mucositis
4. Clarkson et al.	2010	32 Randomized controlled trials	Cochrane risk of bias tool	SR and MA	Therapeutic interventions for oral mucositis
5. Gibson et al.	2010	54 randomized controlled trials	Not cited	RS	Assessment tools for pediatric oral mucositis
6. Hong et al.	2010	64 studies (observational interventional)	The American Society of Clinical Oncology of the American Society of Clinical Oncology Practice.	RS	Prevalence of caries, Prevalence of periodontal disease, Prevalence of dental infections in cancer patients
7. Gawade et al.	2013	47 (observational studies, clinical trials, reviews, case series)	The agency for research and quality in health.	RS	Long-term oral complications of cancer therapy in childhood cancer survivors
8. Mcguire et al.	2013	52 research studies research	The criteria of Somerfield et al.	RS	Prophylactic and therapeutic interventions for oral mucositis
9. Qutob et al.	2013	27 clinical trials	The list of Fetcher et al	RS	Agents for the prevention of pediatric oral mucositis
10. Morais et al.	2014	8 controlled clinical trials	Not cited	RS	Oral complications of chemotherapy in children
11. Oberoi et al.	2014	18 randomized clinical trials	The instruments of the Cochrane Collaboration	SR and MA	The effects of prophylactic low intensity laser on oral mucositis
12. Manzi et al.	2015	23 controlled clinical trials	The Jadad scale and the Cochrane	RS	Prophylactic interventions for

			risk of bias instrument		oral mucositis induced by outpatient chemotherapy
13. Macedo et al.	2015	6 original studies	Not cited	RS	Chlorhexidine for the treatment of oral mucositis in patients with acute leukemia
14. Hashemi et al.	2015	30 original studies	Not cited	RS	Mouthwash in the prevention of chemo-induced mucositis in children.
15. Elad et al.	2016	41 original studies	Hadorn and Somerfied	RS	Diagnostic and therapeutic tools for oral herpes infection.
16. Hong et al.	2017	59 Cohort studies	Hadorn and Somerfied	RS	Prevalence of dental infections and strategies to prevent dental complications in cancer patients
17. He et Al.	2017	8 randomized controlled trials	The Cochrane Collaboration tool	SR and MA	The effects of low-level laser on chemo-induced pediatric oral mucositis
18. Busenhart et al.	2018	15 non-randomized case-control studies and randomized studies	Cochrane Risk of Bias Tool/ Newcastle Ottawa Scale	SR and MA	Oral complications in children undergoing chemotherapy
19. Mazhari et Al.	2018	9 clinical trials/retrospective studies	Score of Jadad	SR and MA	Prophylactic and therapeutic agents for pediatric oral mucositis
20. Villafuerte et al.	2018	17 observational studies	Echelle Newcastle -Ottawa	RS	Oral microflora during chemotherapy
21. Anschau et Al.	2019	5 randomized clinical trials	The GRADE system	SR and MA	Therapeutic effect of low intensity laser on oral mucositis
22. Ariyawardana et al.	2019	11 clinical trials	Hadorn's criteria	RS	Anti-inflammatory agents in the prevention/treatment of oral mucositis in cancer patients
23. Beek et al.	2019	12 cohort/ randomized controlled trials	The Quality in Prognostic Studies Tool (QUIPS)	RS	Efficacy of leucovorin (LV) therapy in reducing oral mucositis in children with acute lymphoblastic leukemia
24. Hong et al.	2019	17 randomized controlled trials, comparative studies,	Somerfield's criteria and Hadorn	RS	Basic oral care interventions for prevention and/or treatment of

		non-comparative studies			oral mucositis.
25. Seremidi et Al.	2019	16 retrospective studies non-randomized	Newcastle Ottawa Scale	SR and MA	Long-term dental effects of any antineoplastic therapy (except hematopoietic transplantation) for any type of pediatric cancer
26. Yarom et Al.	2019	29 clinical trials	Somerfield's criteria	RS	Effects of vitamins, minerals, dietary supplements on oral mucositis.
27. Zadik et Al.	2019	33 clinical trials (randomized, non-randomized)	Somerfield and Hadorn criteria	RS	Photobiomodulation agents in the prevention and treatment of oral mucositis
28. Peng et al.	2020	29 randomized controlled trials	JADAD Scale and GRADE System	SR and MA	Effects of prophylactic and therapeutic low-intensity laser on oral mucositis
29. Wardil et al.	2020	113 observational studies (prospective and retrospective)/randomized controlled trials.	Not cited	RS	Risk factors for the occurrence of oral mucositis secondary to cancer therapy
30. Gabriel et al.	2021	19 observational studies	Joanna Briggs Institute - University of Adelaide -JBI Manual for Evidence Synthesis	SR and MA	Risk factors associated with the development of oral mucositis in children with cancer

SR: systematic review **MA: meta-analysis**

Table II: PICO characteristics of included systematic reviews

Systematic review	Pediatric population	Exposure	Comparators	Outcomes	Findings
1. Worthington et al. (2002)	Not cited (Only one pediatric study)	Oral prophylactic agents	- Placebo/no treatment	Cryotherapy may have a beneficial effect in the prevention of mucositis. The use of antifungal agents that are partially or fully absorbed from the gastrointestinal tract can reduce the incidence of oral candidiasis.	There is weak and unreliable evidence that cryotherapy prevents mucositis. The use of antifungal agents, which are absorbed or partially absorbed by the gastrointestinal tract, has been shown to reduce the clinical signs of candidiasis.
2. Napeñas et al. (2007)	Not cited (4 pediatric studies)	Chemotherapy	- Healthy group	The change in oral bacteria noted in the pediatric studies involved: G+ Streptococci and Staphylococci. No association between oral mucositis and change in flora was revealed.	Further research is needed to determine the relationship between the nature and extent of oral microflora, the degree of granulocytopenia, and the presence of mucositis in patients receiving chemotherapy.
3. Tomlinson et al. (2008)	653 (14 pediatric studies)	Elements of the mucositis assessment scale in children	-Adult Mucositis rating Scale	The objective elements of the scale can be evaluated differently, hence the interest in training the evaluators. Concerning the subjective elements, there is a controversy between including pain or excluding it because it is influenced by the use of analgesics. The functional elements reflect limitations in the mucositis assessment scale.	It is always necessary for investigators to carefully select the method of assessing oral mucositis in clinical trials. Obtaining the opinions of experts in pediatric mucositis will optimize the widespread acceptance of such a scale.
4. Clarkson et al. (2010)	141 enfants (4 pediatric studies)	Benzydamine Low intensity laser Sucralfate	- Placebo - Fictitious Laser - Placebo	There is limited evidence that low-level laser treatment is beneficial in reducing the severity of mucositis. There is no evidence that patient-controlled analgesia is better than continuous infusion for pain control. There is unreliable evidence that pain duration is slightly reduced with patient-controlled analgesia.	Well-designed, placebo-controlled or no-treatment trials evaluating the effectiveness of the interventions studied in this review and new interventions for the treatment of mucositis are needed.
5. Gibson et al. (2010)	Not cited (4 pediatric studies)	Instruments for the evaluation of mucositis in	- Adult Mucositis rating Scale	1 single instrument (Eiler's OAG) useful in the field of children and youth with cancer. This instrument has been described as clinically useful for	A universally accepted standard, validated and reliable scoring system, especially for use with children, is still

		children		assessing oral cavity status, determining changes, and guiding nursing interventions in pediatric cancer care.	far from being achieved. The need to use a validated and reliable instrument in future clinical trials cannot be underestimated.
6. Hong et al. (2010)	Not cited (12 pediatric studies)	The prevalence of dental caries, periodontal disease, and dental infections in cancer survivors during treatment.	- Post-radiotherapy patients - Post-chemotherapy patients - Healthy group	1-Patients who were post-radiotherapy had a higher CAD index compared to those who were post-chemotherapy. 2. Patients who were undergoing post-antineoplastic treatment had a higher plaque and gingival index than healthy patients. 3. The use of fluoride products and chlorhexidine rinses are beneficial in post-radiotherapy patients. 4. Conventional glass ionomer restorations are performed less frequently than resin-modified glass ionomer, composite and amalgam in post-radiation patients. 5. There is still a lack of clinical studies on the extent and severity of dental disease associated with infectious complications during cancer treatment.	The results of this study cannot be extrapolated to patients undergoing radiation therapy. There are currently no studies that have evaluated which dental treatment protocol may be most appropriate in patients undergoing radiation therapy.
7. Gawade et al. (2013)	1330 children,	The description of late effects in cancer cancer survivors.	- Patients undergoing chemotherapy - Patients undergoing radiotherapy - Patients with hematopoietic cell transplantation - Control group	Younger age at treatment, higher radiation dose, and treatment with radiation, chemotherapy, and hematopoietic cell transplantation (HCT) appear to be associated with an increased risk of agenesis, dental hypoplasia, and growth retardation. Fortunately, the risk of caries occurrence among survivors treated with HCT or chemotherapy has decreased over time as regular and individualized preventive dental care has been implemented. Recent studies have reported an increased risk of dental abnormalities in people treated with alkylating chemotherapy agents, specific to age and dose.	Further studies are needed to characterize late dental effects and associated risk factors in survivors treated with salivary gland-sparing intensity-modulated radiation, targeted chemotherapy, and when performing preventive dental care before, during, and after cancer treatment. Studies are also needed to assess the change in risk of cardiovascular morbidity and mortality in association with dental care in survivors. Investigations assessing the effects of diet, oral hygiene, and genetics on

					dental abnormalities may improve the accuracy of identifying survivors at risk for late dental effects.
8. Mcguire et coll.(2013)	Not cited	Oral and dental care protocols, saline solution, sodium bicarbonate, Combination drug mouthwash, chlorhexidine and calcium phosphate	----	- The use of oral care protocols in the prevention of mucositis in all age groups and in all treatment modalities. -Do not use chlorhexidine for the prevention of mucositis in patients with head and neck cancer receiving radiotherapy. -For all other interventions, no formal guidelines were possible, but based on expert consensus, two interventions (normal saline solution and sodium bicarbonate) have been considered harmless and when included in tooth brushing practices can help maintain oral hygiene and promote patient comfort. - Dental care by professionals has important positive attributes, in particular the reduction of local infections. - Mixed drug mouthwash has some limitations.	A persistent gap in the body of research to support evidence-based use of most of the interventions that were reviewed. Thus, further research is clearly needed to generate much-needed evidence to support future clinical practice guidelines.
9. Qutob et coll.(2013)	Not cited (27 pediatric studies)	Prophylactic agents for the prevention of oral mucositis in children.	- Control group	-Oral care protocols should be considered effective, feasible ways to prevent oral mucositis in children. 2-Sucralfate oral suspensions, prostaglandin E2 tablets should not be considered for the prevention of oral mucositis in children. -Evidence of the use of mouthwash at the chlorhexidine (only without conjunction with an oral care protocol), laser therapy, and glutamine to prevent oral mucositis in need of further investigation and should not be considered in the prevention of oral mucositis in the child.	The presence of difficulties related to standardizing all the variables to conduct studies among children cancerous. These variables include many risk factors associated with the development of oral mucositis, including genetic predisposition. This genetic predisposition as well as other risk factors have not been studied in children due to the low incidence of childhood cancer and due to familial susceptibility issues when it comes to clinical trials. involving their children.
10. Morais et al. (2014)	472 children	Oral complications in children with acute lymphoblastic	- Control group	The results of studies have shown that most patients with ALL develop oral lesions during or after the start of chemotherapy.	The oral health status of patients with ALL varies according to a number of factors.

		leukemia (ALL) on chemotherapy (description, incidence)			Further studies are needed to better elucidate this topic, particularly with respect to the prevention and control of these oral manifestations.
11. Oberoi et al. (2014)	Not cited (only 1 pediatric study)	Low Level Laser Therapy (LLLT) (internal or external) administered in prophylaxis of oral mucositis with any intensity, power, wavelength, energy density.	- Placebo/no treatment	-Prophylactic LLLT reduced the risk of the occurrence of severe mucositis compared with placebo or no treatment. -Prophylactic LLLT also reduced the overall mean grade of mucositis and the duration of severe mucositis. -A reduction in the incidence of severe pain, overall mean pain scores and the proportion of patients requiring opioid analgesia was noted. - LLLT reduced unplanned radiation interruptions in patients with head and neck cancer. -Prophylactic LLLT reduces severe mucositis and pain in cancer patients and hematopoietic transplant recipients.	Future research should identify the optimal characteristics of LLLT and determine its feasibility in the clinical setting.
12. Manzi et al. (2015)	Not cited	Any agent, used by itself or in combination, as prophylaxis of oral mucositis in antineoplastic therapy	-Standard hygiene agent -Placebo -No intervention	-Cryotherapy is a potential prophylactic intervention for oral mucositis in patients receiving chemotherapy.	Other interventions such as glutamine, oral care, palifermin, allopurinol, and chlorhexidine have shown positive results in preventing oral mucositis, but further studies are needed to confirm their findings. More prospective and well-defined studies evaluating the efficacy of prophylaxis in chemotherapy-induced oral mucositis are needed to support the actions of the nurse and promote professional practice based on evidence-based science.

13. Macedo et al. (2015)	82 (4 pediatric studies)	Prevention and treatment of oral mucositis with chlorhexidine gluconate	-Bicarbonate of soda -Povidone iodine -Zinc sulfate -No intervention	Chlorhexidine does not completely eliminate oral mucositis, but is able to decrease its frequency and intensity without significant adverse effects for patients, also decreasing pain and discomfort.	It is important that further studies be conducted as other drugs besides chlorhexidine may have better results.
14. Hashemi et al. (2015)	Not cited (only pediatric studies)	Basic oral interventions (chlorhexidine, sodium bicarbonate, benzydamine, saline, saline, granulocyte-macrophage colony stimulating factor, iseganan) for the prevention of oral mucositis (OM) in cancer patients undergoing chemotherapy.	-Saline solution -Honey -Placebo -Cryotherapy -Sucralfate mouthwash	Chlorhexidine, saline, sodium bicarbonate, iseganan, benzydamine, sucralfate, and granulocyte macrophage colony-stimulating factor have been used as mouthwashes for the prevention of chemotherapy-induced mucositis. However, none of these mouthwashes have been shown to be truly effective.	Several investigations have been conducted on the efficacy of mouthwashes containing cytokines, antibacterial and anti-inflammatory agents, etc., for the prevention of chemotherapy-induced oral mucositis. However, further investigations are needed in order to publish practical guidelines in this context.
15. Elad et al. (2016)	Not cited	Measuring herpes viral infections in patients with cancer	----	Aciclovir and valaciclovir are effective in the management of oral herpes infections in patients receiving cancer therapy.	Considering the variability of outcome measures reported to assess oral herpetic infections, the investigator must carefully select appropriate measures based on the purpose of the study. Studies of new antiviral drugs may be useful in addressing the problem of resistance.
16. Hong et al. (2017)	154 children (2 pediatric studies)	Prevalence of odontogenic infections and effectiveness of dental strategies to prevent dental	- Control group	The prevalence of dental infections and pericoronitis during cancer treatment was 5.4 and 5.3%, respectively. The frequency of dental infections during intensive chemotherapy after complete, partial, and minimal	There have been no randomized clinical trials of dental assessment/treatment protocols prior to initiation of cancer therapy because it is ethically unacceptable to withhold care from cancer patients in a

		complications in cancer patients (all ages)		pre-cancer dental evaluation during treatment protocols ranged from 0% to 4%. (Results not specific to children)	prospective study.
17. He et al(2017)	373 children	Low intensity laser delivered intra-orally or extra-orally (red or infrared) to prevent or treat oral mucositis in any wavelength, intensity, power or energy, density.	- Placebo (in prevention) - Routine care (in treatment)	Prophylactic low-intensity laser reduces the occurrence of mucositis in pediatric and young cancer patients. Therapeutic low-intensity laser also reduces the average severity of mucositis and oral pain.	More research should investigate the optimal parameter of the low-intensity laser in pediatric and young patients. Studies with higher quality methodology should be performed.
18. Busenhart et al(2018)	2315 children	Adverse dental effects associated with chemotherapy in children with cancer	- Control group	Chemotherapy was significantly associated with an increased risk of tooth discoloration, arrested tooth development, enamel hypoplasia, microdontia, premature apexification, and decreased salivary flow, and poor oral hygiene.	The strength of the evidence was very low because of the inclusion of non-randomized studies with a high risk of bias
19. Mazhari et al(2018)	504 children	The effect of low-intensity laser and palifermin in the prevention/treatment of oral mucositis induced by cancer therapies.	- Placebo	Palifermin significantly reduced the incidence, duration and severity of oral mucositis in pediatric cancer patients significantly. However, laser did not show significant efficacy in reducing the incidence rate of mucositis.	No particular intervention can be considered a gold standard for the prevention and treatment of mucositis. Of the various agents examined in the present study, the available evidence supported the palifermin protocol only.
20. Villafuerte et al(2018)	296 children (5 pediatric studies)	Changes in the oral microorganism or oral flora (quantitative and qualitative) during chemotherapy	- before and after chemotherapy	In general, studies in pediatric patients isolated more Gram-positive bacteria than studies in adult patients, which isolated more Gram-negative bacteria.	Despite the limitations of the study, it can be concluded that cancer patients may present a more complex oral microbiota under conditions favorable to their development during immunosuppression, and this may be responsible for various serious local or systemic pathologies.

21. Anschau et al(2019)	146 children (2 pediatric studies)	The low intensity laser for the treatment of oral mucositis.	- Control group	There is moderate evidence that low-intensity laser is effective in curing oral mucositis lesions in adult cancer patients. Although there is not enough evidence to point to effectiveness in the curative treatment of mucositis in children.	There are limitations to this conclusion related to the potential risk of bias and the fact that we found few randomized clinical trials in the literature specifically addressing this curative laser treatment, which led to a lower robustness of results.
22. Ariyawardana et al(2019)	347 (few studies in children)	Anti-inflammatory agents in the prevention/treatment of oral mucositis in cancer patients	- Chlorhexidine Povidone iodine Sodium bicarbonate	Benzydamine mouthwash is the only anti-inflammatory drug proven to prevent oral mucositis. This systematic review confirmed the existing guideline on the use of benzydamine mouthwash for the prevention of radiation-induced mucositis in patients with head and neck cancer. The panel also suggested the use of benzydamine mouthwash for patients with head and neck cancer receiving radiotherapy-chemotherapy.	Additional well-designed research is needed on other interventions (classes of agents) and in other cancer treatment settings.
23. Beek et al(2019)	1234 children	The efficacy of different leucovorin (LV) therapy regimens in reducing oral mucositis in children with acute lymphoblastic leukemia after high dose methotrexate (MTX).	- Different doses of Leucoverine and different times of administration	Less oral mucositis in high-dose methotrexate regimens combined with leucoverine (LV) therapy in which higher cumulative doses of LV were administered and when LV was initiated early after high-dose methotrexate administration	More studies specifically designed to determine the most optimal dosage and timing of VL therapy are needed. The effect of baseline folate levels on the development of MTX-induced oral mucositis remains unclear.
24. Hong et al(2019)	Not cited	Basic oral health care interventions for prevention and/or treatment of oral mucositis.	- Chlorhexidine - Placebo	-Based on the literature, the following guidelines were possible. The panel suggests that the implementation of a combination of oral oral protocols are beneficial for the prevention of oral mucositis during chemotherapy, head and neck radiation therapy (RT), and hematopoietic stem cell transplantation. -The panel suggests that chlorhexidine should not be used to prevent mucositis in patients undergoing head and neck radiotherapy.	This systematic review highlights the importance of a multidisciplinary approach, where medical, dental, and nursing professionals as well as patients elaborate to formulate a clinical pathway for the management of cancer treatment-associated mucositis in institutions. Patient education to improve oral hygiene is a new intervention that has been added to the guidelines.

				-No guidelines were available for professional oral care, patient education, use of saline and sodium bicarbonate. Expert opinion supplemented these guidelines.	
25. Seremidi et al(2019)	1458 children	The long-term dental effects of any antineoplastic therapy (except hematopoietic transplantation) for any type of pediatric malignancy that included a combination of radiation and chemotherapy.	-----	The results of this review showed that among cancer survivors: 1. Root defects are more common than crown defects. 2. The most common root defect is impaired root growth. 3. The most common coronal defect is microdontia. 4. Younger age at diagnosis, higher radiation dose and total body irradiation are statistically associated with a higher prevalence of dental defects.	Advanced research should focus on addressing patient factors (oral hygiene, diet, and genetics) as well as environmental factors (radiation and chemotherapeutic agents) to allow for proper screening and early identification of survivors at risk for developing late dental defects. Additional evidence is needed on new treatment modalities, including intensity-modulated radiation therapy (IMRT) and targeted chemotherapy to study dental delays, effects, and associated risk factors in survivors. One of these new treatment modalities, IMRT, has been proposed to minimize late complications because it delivers high doses of radiation to the tumor site while minimizing the doses delivered to the surrounding normal tissue.
26. Yarom et al (2019)	168 children	The usefulness of vitamins, minerals, dietary supplements in the management of oral mucositis.	- Chlorhexidine - Placebo	-A new suggestion has been made opting for the use of oral glutamine for the prevention of oral mucositis in head and neck cancer receiving radiotherapy with concurrent chemotherapy. -The previous recommendation against the use of parenteral glutamine for the prevention of oral mucositis in hematopoietic stem cell transplant patients was maintained. -The previous suggestion to use zinc for the prevention of oral mucositis in patients with head	Of the vitamins, minerals, and nutritional supplements studied for the management of oral mucositis, the evidence supports a recommendation against parenteral glutamine in hematopoietic cell transplant patients and a suggestion in favor of oral glutamine in head and neck cancer for the management of oral mucositis.

				and neck cancer treated with radiation or chemoradiotherapy was rejected because of the lack of a possible guideline. -No guidelines were available for the other interventions.	
27. Zadik et al (2019)	Not cited (4 pediatric studies)	Management of oral mucositis by photobiomodulation.	-No intervention	-Evidence supports the use of specific photobiomodulation therapy (PBM) parameters for the prevention of oral mucositis in specific patients. -In these circumstances, PBM is recommended for the prevention of oral mucositis. The guidelines are subject to update based on new published data.	Clinical trials have reported highly variable endpoints, limiting the integration of data. Recommendations are made for the prevention of mucositis and associated pain with photobiomodulation therapy in cancer patients treated with one of the following modalities: hematopoietic stem cell transplantation, head and neck radiation therapy (without chemotherapy), and head and neck radiation therapy with chemotherapy. For each of these modalities, the authors recommended 1 to 2 clinically effective protocols; the clinician must adhere to all parameters of the selected protocol. Due to insufficient evidence, currently, no possible established guideline for the management of chemotherapy-related oral mucositis.
28. Peng et al(2020)	Not cited (10 pediatric studies)	Low-intensity laser for prophylaxis and therapy in the management of severe oral mucositis in patients undergoing chemotherapy or radiotherapy.	- Control group	Prophylactic low-intensity laser reduced the overall risk of occurrence of severe mucositis (relatively). Therapeutic low-intensity laser significantly reduced the duration of oral mucositis. Low-intensity laser also reduced the overall mean grade of oral mucositis, the overall incidence of severe pain, the mean pain score, and the incidence of severe oral mucositis at the most expected time.	Based on the results of the risk of bias and heterogeneity assessment, the authors believe that better designed multicenter randomized trials on this topic are needed. The uncertain influences of different laser parameters and laser programming schedules indicate the need to determine the optimal laser setting, which should be the goal of

					future studies.
29. Wardil et al(2020)	Not cited	The risk factors for the occurrence of oral mucositis secondary to anticancer treatment.	----	-The highest level of evidence supported dosimetric parameters as key predictors of the risk of mucositis occurrence. -Genetic variants in drug metabolism pathways, immune signaling, and cellular injury/repair mechanisms were also identified as impacting mucositis risk. -Individual factors were variably related to mucositis outcomes, although female gender and smoking status showed some association with risk of mucositis occurrence.	The vast majority of studies rely on hypothesis-driven, single-candidate approaches. Coordinated research efforts with multiple robust approaches are strongly advised to achieve meaningful advances in providing personalized supportive care.
30. Gabriel et al(2021)	2784 children	Risk factors associated with the development of oral mucositis in children with cancer	----	-Chemotherapeutic agents were potential risk factors for oral mucositis in eight (42%) studies. -Hematologic, hepatic, and renal parameters were also considered in eight studies (42%), while specific individual factors were reported in five (26.3%) studies. -Baseline disease, oral microbiota, genetic profile and biomarkers were reported in four (21.5%) studies each. -Meta-analyses showed that the chemotherapy groups had an increased risk factor for the occurrence of mucositis.	More studies are needed in pediatric oncology to standardize risk factor assessment and rating scales for oral mucositis.

3. Qualitative assessment of risk of bias of included studies: (Table III)

4.

Good inter-examiner reliability at risk of selection bias was recorded (kappa score 1.000).
Only one included systematic review fully met the AMSTAR 2 criteria [34]. A total of nine had low quality [18 ,23,24, 31,32,33,35,37,38] and twenty were assessed as having critically low quality [9,10,11,12,13,14,15,16,17,19,20,21,22,25,26,27,28,29,30,36]

Table III: Qualitative assessment of risk of bias of included systematic reviews

Name of authors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Quality of the review
Worthigton et al (2002)	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	**low**
Napenas	Y	N	Y	N	N	N	N	Y	N	N	-	-	N	N	-	N	**Critically low**
Thomlison	Y	N	N	N	N	N	N	N	N	N	-	-	N	N	-	N	**Critically low**
Clarkson	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**high**
Gibson	Y	N	N	PY	Y	Y	N	N	N	N	-	-	N	N	-	N	**Critically low**
Hong 2010	Y	N	N	N	Y	Y	N	N	N	N	-	-	N	N	-	Y	**Critically low**
Gawade	Y	N	N	PY	N	Y	Y	PY	N	N	-	-	N	N	-	Y	**Critically low**
Mcguire	Y	PY	N	N	Y	Y	N	N	N	N	-	-	N	N	-	Y	**Critically low**
Qutob	Y	N	N	PY	N	N	N	N	N	N	-	-	N	N	-	Y	**Critically low**
Morais	Y	N	N	PY	Y	Y	N	PY	N	N	-	-	N	N	-	Y	**Critically low**
Oberoi	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	**Low**
Manzi	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	**Low**
Macedo	Y	N	N	PY	Y	Y	N	PY	N	N	-	-	N	N	-	Y	**Critically low**

Hashemi	Y	N	N	Y	N	N	N	N	N	N	-	-	N	N	-	N	**Critically low**
Elad	Y	N	N	PY	Y	Y	Y	N	N	N	-	-	N	N	-	Y	**Critically low**
Hong 2017	Y	N	Y	PY	Y	Y	N	PY	N	N	-	-	N	N	-	Y	**Critically low**
He	Y	N	Y	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y	**Critically low**
Busenhart	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	**Low**
Manzhari	Y	N	Y	Y	Y	Y	PY	N	PY	Y	Y	Y	Y	Y	Y	Y	**Low**
Villafuerte	Y	N	N	PY	Y	Y	N	Y	Y	Y	-	-	Y	Y	-	Y	**Critically low**
Anschau	Y	PY	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	**Low**
Ariyawardana	Y	PY	Y	Y	Y	Y	N	PY	N	N	-	-	N	N	-	Y	**Critically low**
Beek	Y	N	N	PY	Y	Y	N	Y	Y	N	-	-	Y	N	-	Y	**Critically low**
Hong 2019	Y	PY	Y	Y	Y	Y	N	PY	N	N	-	-	N	Y	Y	Y	**Critically low**
Seremidi	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	**Low**
Yarom	Y	PY	Y	Y	Y	Y	N	PY	N	N	-	-	N	N	-	Y	**Critically low**
Zadik	Y	PY	Y	Y	Y	Y	N	PY	N	N	-	-	N	N	-	Y	**Critically low**
Peng	Y	Y	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	**Low**
Wardil	Y	N	N	PY	Y	Y	N	N	N	N	-	-	N	N	-	Y	**Critically low**
Gabriel	Y	Y	Y	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y	**low**

Y : Yes N : No PY : Partilly Yes - : No meta-analysis done

Discussion

1. Discussion of Methodology:

This "umbrella review" qualitatively summarizes the included systematic reviews containing the evidence accumulated until now on oral manifestations of cancer therapies in children.

The methodological quality of the included systematic reviews ranged from low to critically low, and thus the current evidence is far from high confidence. The main conclusion is the importance of prevention, as the available evidence on prevalence, description and management is still very heterogeneous. This review is very relevant given the relatively large number of systematic reviews published in recent years, indicating the importance and relevance of this topic. Moreover, it is considered among the first "Umbrella reviews" on the oral manifestations of antineoplastic therapies in children.

2. Strengths and Limitations:

Our Umbrella review has several strengths:

- It provides an overview of available published systematic reviews of oral events related to cancer therapy in children using a transparent methodology.
- It allows following the evolution of the knowledge about the events over time due to the change of antimitotic protocols.
- It allows to follow the evolution of the different preventive and therapeutic interventions that have or have not proven to be effective in the field of oral complications of antineoplastic therapies in children

However, it is essential to note certain weaknesses that are not essentially related to the methodology of the umbrella review but rather to the lack of scientific evidence in the conclusions we were able to draw from the included systematic reviews (low to very low methodological quality according to AMSTAR 2).

3. Discussion of Results

3.1. Incidence/prevalence of different oral manifestations:

According to our investigation, the most evaluated oral manifestation in the systematic reviews we included was oral mucositis, due to its predominance in this population under antimitotic therapy. According to a 2007 systematic review by Napenas et al, the incidence of chemo-induced mucositis was reported to be between 30% and 75% depending on the chemotherapy regimen followed [12]. This review included clinical trials, four of which evaluated a pediatric population, however these authors confirmed that there was a lack of standardization in the definition of mucositis, varying from erythema, ulceration, bleeding, petechiae, swelling, viral infection and candidiasis.

Indeed, in the systematic review by Mazhari et al (2018), approximately 80% of children undergoing chemotherapy will experience oral mucositis, with a different incidence depending on the type of cancer and the treatment followed [31]. The studies included in this review were randomized clinical trials and retrospective studies specific to children which made this review subject to considerable risk of bias.

The prevalence of oral manifestations was reported in other systematic reviews and was related to poor oral hygiene of patients and anticancer treatments according to the review by Morais et al [17]. According to the same review, the most common oral lesions were classified as mucositis, candidiasis, periodontitis and gingivitis. The common sites of onset of oral manifestations were oral mucosa and labial mucosa, while the induction phase was considered the time when children undergoing chemotherapy had the most oral manifestations [17].

In India, oral mucositis was the most common manifestation in children (20.6%) , while in Mexico gingivitis was the most common (91.84%). In the United States, children undergoing chemotherapy had a higher risk of developing periodontal disease than caries, which was also confirmed by a study done in Poland [17].
The studies included in this review were both cross-sectional and longitudinal studies conducted entirely in a pediatric population. However, the authors did not provide the limitations of these studies [17].

In the systematic review by Beek et al, the prevalence of oral mucositis was classified by grade with reference to the National Institute of Common Cancer and Toxicity Criteria (NCI-CTC) or the World Health Organization (WHO) and ranged for oral mucositis of a grade ≥3 between 0% and 41% while it was 44% for that of a grade ≥1 [27]. This review performed on a sample of children included retrospective, prospective studies and randomized clinical trials and classified these results as having a "moderate risk of bias" [27]. Apart from oral mucositis, other reviews have evaluated other possible oral manifestations during cancer treatment. Indeed, the systematic review of Hong et al in 2017, focused on the prevalence of dental infections during cancer therapy and which was relatively low (5.4%) [9] compared to that of 2010 according to the same authors (5.8%) [14]. The latter reported from the studies she included several findings:
The overall prevalence of dental caries was 28.1% with a higher prevalence (37.3%) in patients who received chemotherapy only, while the prevalence of dental caries in patients who were post-radiotherapy and those who were post-chemoradiotherapy were 24% and 21.4%, respectively[14].
The overall Cao index (temporary dentition) for children who were on cancer therapies was 3.23[14].
The weighted prevalence of severe gingivitis was assessed on patients undergoing chemotherapy and was 20.3% [14].
The overall plaque index for patients who were on post-antineoplastic therapies was 1.38. This index was 1.46 in post-chemotherapy patients [14].

This same review included both observational and interventional studies, twenty-four of which were in children and four of which included both children and adults. While the limitations of these studies were reported in the fact of the presence of a lack of clinical trials to assess the extent of dental disease associated with complications during cancer treatment, despite the recommendations of the National Health Institute in 1989 for more studies in this area. In addition, these studies had small sample sizes, did not report pre-existing oral conditions, and had varied methodologies, thus drawing a conclusion from these data was biased.

Also, the studies included in the systematic review by Busenhart et al (2018) demonstrated a high prevalence of oral manifestations in children with cancer receiving chemotherapy namely: gingivitis, caries, mucositis, cheilitis, oral pain, periodontitis, recurrent herpes, saliva alteration, xerostomia, and disorders of tooth number or development [23]. This review by Busenhart et al, included retrospective non-randomized studies in children and confirmed the presence of limitations due to the risk of bias that this type of included studies present, in addition to methodological issues that may have influenced the results of the review. Finally, the limited number of included studies (15 studies) did not allow a robust assessment of their heterogeneity [23].

Worthington's 2002 systematic review assessed the incidence of oral manifestations in children and adults, but the authors did not establish an association between gender and the frequency of these manifestations [33]. This systematic review included randomized clinical trials of which only one was conducted in a specific sample of children and five others contained both adults and children in their sample. According to the authors of this review, the eligible trials varied in design and quality with unfortunately seven studies presenting data in an unexploitable form [33].

Only one systematic review by Elad et al in 2016 addressed the prevalence of oral herpetic infection in neutropenic patients which was higher than in patients treated with head and neck radiotherapy (~50% vs 0% respectively) whereas with head and neck radio-chemotherapy the prevalence of oral herpetic infection was about 43% [21]. But unfortunately, none of the included studies was specific to children.

Besides these short-term manifestations, other long-term manifestations appear in cancer survivors as specified in a systematic review done in 2019 by Seremidi et al, including 1300 patients with a mean age at cancer diagnosis of 4.5 years. The results indicated that root defects were more common than coronal defects with a prevalence ranging from 0.5% to 100%. The most common root defect was impaired root growth and agenesis. While the prevalence of coronal defects ranged from 2% to 75%, with the most common defect being microdontia followed by coronal malformations. [38]

However, according to the authors, no index exists to quantify each defect and therefore, the included studies reporting the prevalence of dental outcomes may be invalid. Most of the tools available to quantify outcomes were limited. In addition, pre-existing defects were not accounted for, with the exception of one study, in which the sample included survivors with radiographs before the start of treatment, although the selection of such a sample increased bias, but it allowed for a direct comparison in order to draw specific conclusions about the effect of specific treatment modalities on dental tissue [38].

3.2. Prevention of oral manifestations:

The prevention of oral manifestations caused by cancer therapies was a component addressed by several systematic reviews.

Mucositis, being the most dreaded manifestation in children during cancer therapy, was predominantly addressed in these reviews:

In 2002, Worthigton et al found evidence on the usefulness of cryotherapy in the prevention of oral mucositis and the use of antifungal agents partially or totally absorbed by the gastrointestinal tract in the prevention of oral candidiasis [33]. Another systematic review in 2015 by Manzi et al, confirmed with strong evidence that cryotherapy can prevent oral mucositis resulting from outpatient fluorouracil chemotherapy [18].

Two systematic reviews in 2013 (Qutob et al, Mcguire et al) and a systematic review in 2019 (Hong et al) confirmed the use of oral care and hygiene protocols to prevent oral mucositis across all treatments, antineoplastic modalities, and age groups and invalidated the use of chlorhexidine mouthwash for the prevention of oral mucositis in patients undergoing head and neck radiotherapy [10,16,28]. Also in 2015, the systematic review by Hashemi et al showed that the use of bicarbonate-based mouthwash, iseganan, benzydamine, sucralfate and granulocyte macrophage colony-stimulating factor for the prevention of chemo-induced mucositis was found to be truly ineffective [20].

In contrast to this, a systematic review evaluating the effect of systemic and mouthwash anti-inflammatory drugs in the prevention of antineoplastic therapy-induced mucositis in 2019 (Ariyawardana et al), confirmed that only benzydamine mouthwash was proven to be effective in this area. [26] One of the most recent interventions in the prevention of oral mucositis is prophylactic low-level laser and has been shown to reduce the overall risk of oral mucositis and severe mucositis (grade III or higher) in children undergoing cancer therapies (head and neck radiotherapy with or without chemotherapy, hematopoietic cell transplantation) according to several systematic reviews since 2014 until 2020. [30,31,35,36]

Furthermore, a systematic review in 2018 (Mazhari et al), confirmed that palifermin (growth factor) reduced the incidence, duration and severity of pediatric oral mucositis due to cancer therapies [24]. Another study in 2019 (Yarom et al), reviewing natural agents used for the management of oral mucositis induced by cancer therapies invalidated the use of parenteral glutamine in patients undergoing hematopoietic cell transplantation and confirmed the use of oral glutamine in patients undergoing head and neck radiation therapy to prevent oral mucositis [29].

In Hong et al, prevention of oral complications was primarily achieved through dental assessment/treatment protocols for minor caries and eradication of infectious foci as well as periodontal treatment prior to initiation of cancer therapy for good oral health [14,22]. And for oral herpetic infections, the systematic review by Elad et al in 2016, demonstrated the efficacy of aciclovir (200mg 4 times a day-400mg 5 times a day) and valaciclovir (250mg 2 times a day to 1000mg 3 times a day) in preventing oral herpetic infections caused by cancer therapies with dosage modifications according to age [21].

Indeed, various interventions have been highlighted in children through clinical trials according to the different systematic reviews; however, the authors of these reviews all agreed on the limitations of these studies, namely

- The lack of standardization of scales for measuring oral complications in children with cancer [16, 18].
- The difficulty of conducting clinical trials in a pediatric population because of family sensitivity issues. [16,30,31,38]
- The heterogeneity of study design. [26,36]
- The small sample size included in the studies performed. [18,26]
- And for some interventions such as the low intensity laser despite the success it has presented in studies, the authors have recognized the presence of difficulties regarding the programming and parameters of its use. [30,31]

The systematic reviews by Hashemi et al and Hong et al did not specify the limitations of the studies they included [20, 28].

3.3. Management of oral manifestations:

The majority of systematic reviews have focused on the treatment of oral mucositis in children:
In 2010, Clarkson et al compared three treatments for oral mucositis (benzydamine, sucralate, and the low-intensity laser), they concluded that only the low-intensity laser decreased the severity of oral mucositis [34]. This was consistent with the results of the systematic review by He et al in 2017, which confirmed that low-intensity laser decreased the severity of oral mucositis and its pain [22].

The systematic review by Anschau et al in 2019, showed that although there is not enough evidence to highlight the efficacy in the curative treatment of oral mucositis in children, low-intensity laser has a potential to decrease the time to resolution of mucositis by about 4.21 days [37]. This was also confirmed by Peng et al in 2020 by finding that low-intensity laser therapy significantly reduced the duration of oral mucositis and also reduced the overall mean grade of mucositis, overall incidence of severe pain, mean pain score and incidence of severe oral mucositis, at the most expected time [31].

Also, in the treatment of oral mucositis, a systematic review done in 2019 by Ariyawardana et al, evaluated the usefulness of anti-inflammatory agents and found that benzydamine rinse was more effective, safe and well tolerated by children but could not prove its effect on oral mucositis [26]. Mcguire et al in 2013 and Hong et al in 2019 looked at the role of dental hygiene and care protocols (saline mouthwash, baking soda, chlorhexidine, mixture ...) in the management of oral mucositis and could not prove the efficacy of any of these protocols in treating oral mucositis [10, 28].

Chlorhexidine 0.12% was also evaluated by Macedo et al in 2015 for its therapeutic effect on oral mucositis and was approved in decreasing its frequency and intensity without significant adverse effects in children, reducing pain and discomfort [19]

Another systematic review done in 2019 by Beek et al looked at the usefulness of leucoverin (folinic acid) in the treatment of methotrexate-induced mucositis (in chemotherapy) and showed that the rate of oral mucositis was lower in treatment regimens with cumulative doses of leucovorin and during early initiation of leucovorin after chemotherapy [27].

Hong et al addressed the management of oral complications after antineoplastic treatment in 2010 and 2017 by confirming that the application of fluoride was beneficial in the prevention of dental caries after head and neck radiotherapy and that the use of chlorhexidine mouthwash (0.12% to 0.2%) once or twice a day was also effective in reducing the accumulation of plaque and mutans streptococci after head and neck radiotherapy [14, 22]. While Elad et al in 2016 provided an update on the treatment of oral herpetic infection with the use of aciclovir and valaciclovir and confirmed their efficacy [21].
Several limitations to the included studies in the area of management of oral complications of antimitotic therapies have been revealed namely:

- Lack of randomized clinical trials for curative interventions [19, 27, 34].
- The existence of several assessment scales and measures of oral mucositis [10, 22, 26, 31, 37].
- The lack of studies performed in children [19, 26, 34, 37].

4. Implications for Research:

There are countless recommendations in the literature that can be considered.

- More studies of the child with cancer should be done.
- Future studies should include large numbers of patients with long follow-up periods.
- Perhaps, if there was a well-defined methodology that could be applied to the analysis of the results, the studies would be more comparable and meaningful.
- Randomized clinical trials should be recommended in order to have high level scientific evidence.

Although the systematic reviews included in our Umbrella review have addressed the issue and identified different aspects of oral manifestations in children undergoing antimitotic therapy, only the 2010 systematic review by Clarckson et al. met the qualitative criteria of AMSTAR 2. We can see that more systematic reviews following the same methodology will likely allow us to draw more credible conclusions in this area.

5. Implications for Practice:

Dental evaluation and prophylactic interventions in pre-cancer therapy are recommended and indicated. Given the high incidence of oral mucositis and the significant pain caused by its occurrence despite the evolution of antineoplastic therapies, it is imperative to institute rigorous oral hygiene protocols before the start of any antimitotic intervention. Low-intensity laser has been shown to decrease the severity and duration of mucositis, although more research is

needed in this area, and should be considered in therapeutic and prophylactic interventions for the management of oral mucositis.

Conclusion

In conclusion, despite the evolution of protocols in cancer therapy, oral manifestations related to these therapies still exist with high prevalence. Mucositis remains the most dreaded manifestation and the majority of systematic reviews have insisted on its prevention and management. The other short- and long-term manifestations have also been studied with the aim of reducing their prevalence.

Indeed, although the results of the systematic reviews included in our work are of low quality, we have not been able to assess the quality of the results. This review has allowed us to follow the evolution of oral complications due to antimitotic therapies over time and to specify possible preventive and therapeutic interventions for their management.

Acknowledgement

Miss Ariche Ghizlane, thank you for your English translation and all efforts done in this direction.

Bibliography

1. Sanaa Bensouda, Loubna Benkirane, Zineb EL Jalil, Basma Abiki, Samira El Arabi, “Role of pediatric oncologists in oral care for children undergoing cancer treatment : Study in Casablanca”, IJMSIR- March - 2021, Vol – 6, Issue - 2, P. No. 478
2. Gandhi K, Datta G, Ahuja S, Saxena T,Datta AG. Prevalence of Oral Complications occurring in a Population of Pediatric Cancer Patients receiving Chemotherapy. Int J Clin Pediatr Dent 2017;10(2):166-171.
3. Ritwik P. Dental Care for Patients With Childhood Cancers. Ochsner J. 2018 Winter;18(4):351-357.
4. El Bousaadani A, et al. Actualités de la prévention et du traitement des mucites orales chez les enfants cancéreux : recommandations pratiques. Cancer Radiother (2016)
5. Smith et al.: Methodology in conducting a systematic review of systematic reviews of healthcare interventions.BMC Medical Research Methodology 2011 11:15.
6. R. Sordello, Anne Villemey, A. Jeusset, M. Vargac, Yves Bertheau, et al.. Conseils méthodologiques pour la réalisation d’une revue systématique à travers l’expérience de COHNECS_IT. [Rapport de recherche] irstea. 2017, pp.50.hal-02607263
7. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
9. Gibson F, Auld EM, Bryan G, Coulson S, Craig JV, Glenny AM. A systematic review of oral assessment instruments: what can we recommend to practitioners in children's and young people's cancer care? Cancer Nurs. 2010 Jul-Aug;33(4)
10. McGuire DB, Fulton JS, Park J, Brown CG, Correa ME, Eilers J, Elad S, Gibson F, Oberle-Edwards LK, Bowen J, Lalla RV; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer. 2013 Nov;21(11)
11. Wardill HR, Sonis ST, Blijlevens NMA, Van Sebille YZA, Ciorba MA, Loeffen EAH, Cheng KKF, Bossi P, Porcello L, Castillo DA, Elad S, Bowen JM; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Prediction of mucositis risk secondary to cancer therapy: a systematic review of current evidence and call to action. Support Care Cancer. 2020 Nov;28(11):5059-5073
12. Napeñas JJ, Brennan MT, Bahrani-Mougeot FK, Fox PC, Lockhart PB. Relationship between mucositis and changes in oral microflora during cancer chemotherapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Jan;103(1):48-59.
13. Tomlinson D, Judd P, Hendershot E, Maloney AM, Sung L. Establishing literature-based items for an oral mucositis assessment tool in children. J Pediatr Oncol Nurs. 2008 May-Jun;25(3):139-47.
14. Hong CH, Napeñas JJ, Hodgson BD, Stokman MA, Mathers-Stauffer V, Elting LS, Spijkervet FK, Brennan MT; Dental Disease Section, Oral Care Study Group, Multi-national Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer. 2010 Aug;18(8):1007-21.
15. Gawade PL, Hudson MM, Kaste SC, Neglia JP, Constine LS, Robison LL, Ness KK. A systematic review of dental late effects in survivors of childhood cancer. Pediatr Blood Cancer. 2014 Mar;61(3):407-16.
16. Qutob AF, Gue S, Revesz T, Logan RM, Keefe D. Prevention of oral mucositis in children receiving cancer therapy: a systematic review and evidence-based analysis. Oral Oncol. 2013 Feb;49(2):102-7.
17. Morais EF, Lira JA, Macedo RA, Santos KS, Elias CT, Morais Mde L. Oral manifestations resulting from chemotherapy in children with acute lymphoblastic leukemia. Braz J Otorhinolaryngol. 2014 Jan-Feb;80(1):78-85.
18. Manzi Nde M, Silveira RC, dos Reis PE. Prophylaxis for mucositis induced by ambulatory chemotherapy: systematic review. J Adv Nurs. 2016 Apr;72(4):735-46.
19. Macêdo, Rômulo Augusto de Paiva et al. “Chlorhexidine to treat oral mucositis in patients with acute leukemia: systematic review.” Revista Dor 16 (2015): 221-226.

20. Hashemi A, Bahrololoumi Z, Khaksar Y, Saffarzadeh N, Neamatzade H, Foroughi E. Mouth-rinses for the prevention of chemotherapy induced oral mucositis in children: a systematic review. Iran J Ped Hematol Oncol. 2015;5(2):106-12. Epub 2015 Apr 20.
21. Elad S, Ranna V, Ariyawardana A, Correa ME, Tilly V, Nair RG, Rouleau T, Logan RM, Pinto A, Charette V, Saunders DP, Jensen SB; Viral Infections Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of oral herpetic viral infections in cancer patients: commonly used outcome measures and interventions. Support Care Cancer. 2017 Feb;25(2):687-700.
22. Hong CHL, Hu S, Haverman T, Stokman M, Napeñas JJ, Braber JB, Gerber E, Geuke M, Vardas E, Waltimo T, Jensen SB, Saunders DP. A systematic review of dental disease management in cancer patients. Support Care Cancer. 2018 Jan;26(1):155-174.
23. Busenhart DM, Erb J, Rigakos G, Eliades T, Papageorgiou SN. Adverse effects of chemotherapy on the teeth and surrounding tissues of children with cancer: A systematic review with meta-analysis. Oral Oncol. 2018 Aug;83:64-72.
24. Mazhari F, Shirazi AS, Shabzendehdar M. Management of oral mucositis in pediatric patients receiving cancer therapy: A systematic review and meta-analysis. Pediatr Blood Cancer. 2019 Mar;66(3):e27403.
25. Villafuerte KRV, Martinez CJH, Dantas FT, Carrara HHA, Dos Reis FJC, Palioto DB. The impact of chemotherapeutic treatment on the oral microbiota of patients with cancer: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018 Jun;125(6):552-566.
26. Ariyawardana A, Cheng KKF, Kandwal A, Tilly V, Al-Azri AR, Galiti D, Chiang K, Vaddi A, Ranna V, Nicolatou-Galitis O, Lalla RV, Bossi P, Elad S; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer. 2019 Oct;27(10):3985-3995.
27. Van der Beek JN, Oosterom N, Pieters R, de Jonge R, van den Heuvel-Eibrink MM, Heil SG. The effect of leucovorin rescue therapy on methotrexate-induced oral mucositis in the treatment of paediatric ALL: A systematic review. Crit Rev Oncol Hematol. 2019 Oct;142:1-8.
28. Hong CHL, Gueiros LA, Fulton JS, Cheng KKF, Kandwal A, Galiti D, Fall-Dickson JM, Johansen J, Ameringer S, Kataoka T, Weikel D, Eilers J, Ranna V, Vaddi A, Lalla RV, Bossi P, Elad S; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer. 2019 Oct;27(10):3949-3967.
29. Yarom N, Hovan A, Bossi P, Ariyawardana A, Jensen SB, Gobbo M, Saca-Hazboun H, Kandwal A, Majorana A, Ottaviani G, Pentenero M, Nasr NM, Rouleau T, Lucas AS, Treister NS, Zur E, Ranna V, Vaddi A, Cheng KKF, Barasch A, Lalla RV, Elad S; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO). Systematic review of natural and miscellaneous

agents for the management of oral mucositis in cancer patients and clinical practice guidelines-part 1: vitamins, minerals, and nutritional supplements. Support Care Cancer. 2019 Oct;27(10):3997-4010.
30. Zadik Y, Arany PR, Fregnani ER, Bossi P, Antunes HS, Bensadoun RJ, Gueiros LA, Majorana A, Nair RG, Ranna V, Tissing WJE, Vaddi A, Lubart R, Migliorati CA, Lalla RV, Cheng KKF, Elad S; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer. 2019 Oct;27(10):3969-3983.
31. Peng J, Shi Y, Wang J, Wang F, Dan H, Xu H, Zeng X. Low-level laser therapy in the prevention and treatment of oral mucositis: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Oct;130(4):387-397.e9.
32. De Farias Gabriel A, Silveira FM, Curra M, Schuch LF, Wagner VP, Martins MAT, da Silveira Matte U, Siebert M, Botton MR, Brunetto AT, Gregianin LJ, Martins MD. Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis. Oral Dis. 2021 Mar 28.
33. Worthington HV, Clarkson JE. Prevention of oral mucositis and oral candidiasis for patients with cancer treated with chemotherapy: cochrane systematic review. J Dent Educ. 2002 Aug;66(8):903-11.
34. Rinartha, K., & Suryasa, W. (2017). Comparative study for better result on query suggestion of article searching with MySQL pattern matching and Jaccard similarity. In *2017 5th International Conference on Cyber and IT Service Management (CITSM)* (pp. 1-4). IEEE.
35. Clarkson JE, Worthington HV, Furness S, McCabe M, Khalid T, Meyer S. Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev. 2010 Aug 4;2010(8):CD001973.
36. Oberoi S, Zamperlini-Netto G, Beyene J, Treister NS, Sung L. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis. PLoS One. 2014 Sep 8;9(9):e107418.
37. He M, Zhang B, Shen N, Wu N, Sun J. A systematic review and meta-analysis of the effect of low-level laser therapy (LLLT) on chemotherapy-induced oral mucositis in pediatric and young patients. Eur J Pediatr. 2018 Jan;177(1):7-17.
38. Anschau F, Webster J, Capra MEZ, de Azeredo da Silva ALF, Stein AT. Efficacy of low-level laser for treatment of cancer oral mucositis: a systematic review and meta-analysis. Lasers Med Sci. 2019 Aug;34(6):1053-1062.
39. Seremidi K, Kloukos D, Polychronopoulou A, Kattamis A, Kavvadia K. Late effects of chemo and radiation treatment on dental structures of childhood cancer survivors. A systematic review and meta-analysis. Head Neck. 2019 Sep;41(9):3422-3433.