

# Chlorhexidine to treat oral mucositis in patients with acute leukemia: systematic review\*

## Uso da clorexidina no tratamento da mucosite oral em pacientes com leucemia aguda: revisão sistemática

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\*Received from Potiguar University, Natal, RN, Brazil.

DOI 10.5935/1806-0013.20150044

### ABSTRACT

**BACKGROUND AND OBJECTIVES:** Leukemias impair hematopoietic stem-cells shunting and promote a proliferation of malignant cells without functional competence. Studies point that oral manifestations such as pain, hyperplasia and gum bleeding may be one of the first signs in leukemia patients. In light of the above, this study aimed at carrying out a systematic analysis of articles published in the last 15 years, with regard to chlorhexidine to treat and prevent mucositis in acute leukemia children under chemotherapy.

**CONTENTS:** A systematic search of articles published between January 2000 and January 2015 was carried out in Pubmed/Medline, Science Direct and LILACS databases. After systematic search, 6 articles have fulfilled all methodological inclusion criteria. Chlorhexidine is an important means of preventing and treating oral mucositis and studies refer that 0.12% chlorhexidine gluconate effectiveness is probably related to its bactericide action. Adequate oral hygiene is important to prevent mucositis and other therapeutic modalities have shown to be effective to treat and prevent oral mucositis.

**CONCLUSION:** Chlorhexidine gluconate does not totally eliminate oral mucosa injuries, but is able to decrease their frequency and intensity without significant noxious effects. However, other drugs compared to chlorhexidine in this study may present better results.

**Keywords:** Chemotherapy, Hematology, Oncology, Oral manifestations, Mucositis.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** As leucemias comprometem a derivação das células-tronco hematopoiéticas e promovem uma proliferação de células malignas sem competência funcional. Estudos apontam que manifestações orais como dor, hiperplasia e sangramento gengival podem ser um dos primeiros sinais em pacientes com leucemia. Diante do exposto, o objetivo deste estudo foi realizar uma análise sistemática de artigos publicados nos últimos 15 anos, no que diz respeito ao uso da clorexidina no tratamento e prevenção da mucosite em crianças com leucemia aguda em quimioterapia.

**CONTEÚDO:** Uma busca sistemática de artigos publicados entre janeiro de 2000 e janeiro de 2015 foi feita nas bases de dados Pubmed/Medline, *Science Direct* e LILACS. Após pesquisa sistemática 6 artigos preencheram todos os critérios de inclusão metodológica. A clorexidina é um importante meio de prevenção e tratamento da mucosite oral e estudos referem que a efetividade do gluconato de clorexidina a 0,12% está provavelmente relacionada à sua ação bactericida. A correta higienização oral tem importante papel na prevenção da mucosite e outras formas terapêuticas demonstram ser eficazes no tratamento e prevenção da mucosite oral.

**CONCLUSÃO:** O gluconato de clorexidina não elimina totalmente as lesões de mucosa oral, mas é capaz de diminuir sua frequência e intensidade sem apresentar efeitos deletérios significativos no paciente. Entretanto, outros fármacos comparados à clorexidina neste estudo podem apresentar melhores resultados.

**Descritores:** Hematologia, Manifestações bucais, Mucosite, Oncologia, Quimioterapia.

### INTRODUCCION

Leukemias impair hematopoietic stem-cells shunting and promote a proliferation of malignant cells without functional competence. There are different groups of lymphocytes, thus different types of leukemia, which are classified according to involved cell, disease duration and character<sup>1-4</sup>. Its etiology is still uncertain and might be related to factors such exposure to radiation and genetics<sup>3</sup>.

Acute lymphoid leukemia (ALL) represents approximately 80% of all leukemias affecting children and young adults, and acute myeloid leukemia (AML) is responsible for appro-

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Submitted in May 01, 2015.

Accepted for publication in July 06, 2015.

Conflict of interests: none – Sponsoring sources: none.

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ximately 15% of cases<sup>5,6</sup>. In childhood, most affected age is four years of age, being approximately twice as common in Caucasian patients as compared to non-Caucasians<sup>7,8</sup>. Studies show that oral manifestations such as pain, hyperplasia and gingival bleeding may be the first signs of leukemia patients<sup>4,9</sup>. Treatment of choice for this cancer is chemotherapy, which may be used together with other therapies<sup>10-12</sup>. In the last four decades, there has been major progress in the treatment of leukemia and approximately 80% of children and teenagers with early diagnosis may be cured<sup>8</sup>. However, several studies point to anticancer treatment as inducing oral mucositis<sup>1,2,4</sup>. Oral mucositis is characterized by erythema, followed by very painful ulcers in oral mucosa, which interfere with nutritional status and quality of life (QL), and may limit or even interrupt anticancer therapy in severe cases<sup>2</sup>.

Several studies indicate chlorhexidine gluconate, due to its antibacterial and antifungal activity and binding to tissue surfaces, to prevent and treat oral manifestations of such patients, especially mucositis<sup>2,13</sup>. However, they caution that there may be sequelae for patients with long-term use of chlorhexidine, such as burning sensation, dysgeusia and dental pigmentation<sup>13</sup>.

The understanding of oral injuries caused by acute leukemias (AL) and anticancer therapies is dentists' duty, as well as the use of prophylactic and therapeutic measures to promote patients' oral health and help the return of their physical well-being.

In light of the above, this study aimed at carrying out a systematic analysis of articles published in the last 15 years with regard to the use of chlorhexidine to treat and prevent mucositis in AL children submitted to chemotherapy.

**CONTENTS**

A systematic search of articles published between January 2000 and January 2015 was carried out in Pubmed/Medline, Science Direct and LILACS databases, looking for studies evaluating the use of chlorhexidine to prevent and treat oral mucositis in AL patients.

The following terms were used for the search: Acute Leukemia, Oral Mucositis, Chlorhexidine, Treatment, Prevention, Oral Mucosa, as well as their synonyms and corresponding words in Portuguese and Spanish, in different combinations. Boolean operators AND, OR, NOT were used. Search strategies are shown in table 1.

After getting the abstracts, three independent investigators have selected relevant studies according to inclusion and exclusion criteria. Inclusion criteria were original articles in English, Portuguese or Spanish, aiming at evaluating chlorhexidine to prevent and treat oral mucositis in AL patients; and articles published as of January 2000. Exclusion criteria were clinical cases, review articles, population outside research standards, articles published before 2000 or in different languages from those selected for the study.

The first selection stage was to evaluate titles and abstracts. Then, all studies the titles or abstracts of which were considered relevant to the subject where obtained in whole and completely analyzed. At the end, articles analyzed and selected by evaluators after consensus meeting were included in this review.

After initial search, 15 studies had potential to be included in this study, however after detailed and complete analysis, only 6 have met all methodological inclusion criteria<sup>13-18</sup>. Among selected studies, 5 were performed in developing countries<sup>13-15,17,18</sup> and one in a developed country<sup>16</sup>. Methods and results of evaluated studies are shown in tables 2 and 3.

Participants' sample among selected studies has varied from 14 to 48 patients, in a total of 160 participants. Four studies were performed primarily in children between 2 and 15 years of age<sup>16,17</sup>. Most participants of the studies were above 15 years of age. Oral mucositis prevention and treatment with chlorhexidine gluconate were evaluated by 5 selected studies. Another study has evaluated chlorhexidine gluconate in children with ALL already with oral mucositis<sup>18</sup>.

Intraoral exam was used to evaluate patients of selected studies. Studies<sup>14,16</sup> have used microbiological tests. Pereira Pinto et al.<sup>13</sup> also used cytological exam. Aiming at evaluating pain level of patients, authors<sup>16,18</sup> have used questionnaires applied to participants.

Chlorhexidine gluconate concentration was 0.12%, except for the study by Mehdipour et al.<sup>17</sup> the concentration of which was 0.2%. Three studies had control group without treatment<sup>13,15,17</sup>. Choi & Kim<sup>16</sup> have compared chlorhexidine and sodium bicarbonate to treat oral mucositis and sodium bicarbonate has shown better results.

In the study of Mehdipour et al.<sup>17</sup>, zinc sulfate was compared to chlorhexidine with better results in early evaluations of the study; however there has been no statistically significant difference in the final analysis of the experiment which has lasted 1 month. Setiawan, Reniarti & Oewen<sup>18</sup>, who analyzed the effi-

**Table 1.** Search strategies and number of articles found on databases

Strategies	A	B	C
Chlorhexidine / oral mucositis	12	747	198
Chlorhexidine / oral mucositis / treatment / acute leukemia	0	727	184
Chlorhexidine / oral mucositis / (treatment OR prevention) / acute leukemia	0	733	185
Chlorhexidine / oral mucositis / (treatment OR prevention) / mucosa / acute leukemia	0	531	37
Chlorhexidine / oral mucositis / (treatment AND prevention) / oral mucosa/ acute leukemia	0	401	37

A = LILACS; B = Science Direct; C = Pubmed/Medline.

**Table 2.** Methods and objectives of selected studies

Studies	Objectives	Types of leukemia	n / age	Protocol	Oral health evaluation	Analyzed variables
Soares et al. <sup>14</sup>	Evaluate oral mucosa changes and qualitative microbiota changes in children with ALL under chemotherapy, as well as the use of 0.12% chlorhexidine in such patients.	ALL	17/2 to 12 years.	Chlorhexidine mouthwash for 1 minute, twice a day (30 minutes after lunch and after last meal) for 10 days.	Clinical exam of oral mucosa for detection of oral lesions and microbiological test.	Presence of mucositis; effects of 0.12% chlorhexidine on oral microbiota.
Costa et al. <sup>15</sup>	Check the effectiveness of a preventive oral protocol using 0.12% chlorhexidine mouthwashes in children with ALL submitted to anti-cancer treatment.	ALL	14/2 to 10 years. (7 test group /7 control group).	The experimental group received supervised oral hygiene care and chlorhexidine mouthwash twice a day. The control group received supervised hygiene care with placebo mouthwash twice a day. The experiment started 1 day after and continued for up to 10 days after chemotherapy induction phase.	Clinical oral mucosa exam.	Evaluate the effect of chlorhexidine to treat oral manifestations; compare test and control groups.
Choi & Kim <sup>16</sup>	Compare the efficacy of sodium bicarbonate and chlorhexidine mouthwash to prevent oral manifestations in patients with ALL during chemotherapy induction phase	ALL & AML	48/ Mean of 38 years. (chlorhexidine group=24 patients; sodium bicarbonate group = 24 patients).	Os participantes de ambos os grupos foram orientados a realizar os bochechos 4 vezes ao dia, sendo iniciados 1 dia antes do início da quimioterapia até o final da primeira fase do tratamento oncológico.	Questionnaire, clinical oral mucosa exam and microbiological test.	Presence of oral lesions; effect of mouthwashes on oral mucosa.
Mehdipour et al. <sup>17</sup>	Evaluate the efficacy of zinc oral antiseptic for chemotherapy-induced oral mucositis as compared to chlorhexidine mouthwash	AML	30 (15 Test/15 control) / age above 15 years.	Induction and maintenance phase patients were evaluated. Patients of chlorhexidine and zinc sulfate groups were oriented to use mouthwash twice a day during 14 days. Patients were evaluated for 8 weeks.	Clinical oral mucosa exam.	Compare patients receiving 0.2% zinc sulfate to patients receiving 0.2% chlorhexidine gluconate to prevent oral mucositis
Pereira Pinto et al. <sup>13</sup>	Evaluate clinical aspects of oral mucosa of children with ALL and determine the effect of 0.12% chlorhexidine to prevent oral complications in these patients.	LLA	33 Group I (23 children): Oral 0.12% chlorhexidine solution, 2X/ day, group II (10 children): not receiving solution. /2 to 15 years	The experimental group had chlorhexidine mouthwashes for 1 minute, twice a day (30 minutes after lunch and after the last meal) during 10 days. Control group was not treated.	Clinical oral cavity exam / digital palpation of oral mucosa and cytological swabs (obtained from oral mucosa in the beginning of chemotherapy intensification).	Presence of mucositis; effects of 0.12% chlorhexidine; compare results among study groups.
Setiawan, Reniarti & Oewen <sup>18</sup>	Compare the effectiveness of chlorhexidine gluconate and povidone-iodine mouthwash for oral mucositis in children receiving chemotherapy for ALL.	ALL	18/ 2 to 10 years	Children developing mucositis in the chemotherapy induction phase were evaluated. Group A received 0.12% chlorhexidine, group B povidone-iodine, group C saliva solution. Mouthwashes were performed twice a day (morning and evening) being the protocol repeated every day until injury remission or for a maximum period of two weeks.	Clinical oral mucosa exam.	Evaluate the effects of chlorhexidine gluconate and povidone-iodine on oral mucosa and compare both to control group.

ALL = acute lymphoid leukemia; AML = acute myeloid leukemia.

**Table 3.** Results of studies selected for the research

Studies	More frequent oral manifestations	More frequent manifestation sites	Results
Soares et al. <sup>14</sup>	Mucositis was the most frequent oral manifestation affecting 5 children.	Not mentioned in the study.	Prophylactic use of 0.12% chlorhexidine gluconate decreases the frequency of mucositis and oral pathogens in ALL children under chemotherapy.
Costa et al. <sup>15</sup>	One experimental group (14.3%) and one control group (71.4%) child developed oral mucositis.	Most frequent in lip and jugal mucosa.	There has been significant decrease in the incidence of mucositis and oral ulcers in children with prophylactic chlorhexidine mouthwash.
Choie Kim <sup>16</sup>	Six (25%) patients of the sodium bicarbonate group have developed mucositis versus 15 (62.5%) of the chlorhexidine group.	Not mentioned in the study.	Sodium bicarbonate was more effective as compared to chlorhexidine to fight oral mucositis.
Mehdipour et al. <sup>17</sup>	Frequency of mucositis varied according to exams performed. 1 <sup>st</sup> exam (0 – zinc sulfate / 2 chlorhexidine); 2 <sup>nd</sup> exam (3 zinc sulfate / 8 chlorhexidine); 3 <sup>rd</sup> exam (5 zinc sulfate / 8 chlorhexidine); 4 <sup>th</sup> exam (3 zinc sulfate / 6 chlorhexidine)	Not mentioned in the study.	Zinc sulfate was better to control oral mucositis as compared to chlorhexidine in initial weeks, without statistically significant difference in the last exam.
Pereira Pinto et al. <sup>13</sup>	Mucositis was observed in six group I and eight group II children and was characterized by the presence of edema, erythema and ulcers.	Not mentioned in the study.	Chlorhexidine was beneficial in decreasing oral manifestations in children.
Setiawan, Reniartie Oewen <sup>18</sup>	All children had oral mucositis in the beginning of the study.	Not mentioned in the study.	The study showed that mucositis and related pain presented remission in 5 to 7 days for the chlorhexidine solution group, 8 to 14 days for the povidone-iodine group and 13 to 14 days for the control group.

ALL = acute lymphoid leukemia.

**Table 4.** Chemotherapeutic agents and chemotherapy phases

Studies	Chemotherapeutic agents
Soares et al. <sup>14</sup>	Combinations for chemotherapeutic treatment were not mentioned.
Costa et al. <sup>15</sup>	Therapy consisted of 6-mercaptopurine (one 50/mg/m <sup>2</sup> /day oral dose during six weeks), methotrexate (one 2mg/m <sup>2</sup> intravenous dose in continuous infusion during 24 h in days 1, 15, 30 and 45 of treatment, respectively), leucovorin (one 15mg/m <sup>2</sup> oral dose four times a day in days 2, 3, 16, 17, 31, 32, 46 and 47) and spinal MADIT (combination of 12 mg methotrexate + 70mg cytosine-arabinoside + 2 mg/m <sup>2</sup> dexamethasone) in days 1, 15, 30 and 45.
Choie Kim <sup>16</sup>	Under induction chemotherapy with idarubicin and enocitabine or LLA cyclophosphamide, vincristin and daunorubicin.
Mehdipour et al. <sup>17</sup>	Citarabine in the induction phase and novantrone in the consolidation phase.
Pereira Pinto et al. <sup>13</sup>	Protocol for acute leukemia treatment proposed by the Brazilian Society of Pediatric Oncology <sup>16</sup> . Methotrexate was a drug used in this therapy. 0.12% chlorhexidine gluconate was administered for 10 consecutive days, after each methotrexate infusion during intensification chemotherapy.
Setiawan, Reniartie Oewen <sup>18</sup>	Methotrexate (one spinal dose in days 1, 14 and 42), Dexamethasone (one 6mg/m <sup>2</sup> /day oral dose during 5 weeks), vincristin (one 1.5mg/m <sup>2</sup> intravenous dose in continuous infusion in 5 minutes in days 7, 14, 21, 28, 35), and L-asparaginase (one 6000ug/m <sup>2</sup> intravenous dose in weeks 4 and 5).

MADIT = methotrexate, cytarabine and dexamethasone.

cacy of chlorhexidine and povidone-iodine to treat mucositis, have observed that the chlorhexidine group had faster lesion remission as compared to the second group.

With regard to oral mucosa site most affected by mucositis, only one study of Costa et al.<sup>15</sup> has reported this frequency, being jugal mucosa and lip the sites reported by the authors. Chemotherapeutic drugs used during patients' follow-up period are shown in table 4. Only the study by Soares et al.<sup>14</sup> has not informed the chemotherapeutic scheme used for anticancer therapy. Selected studies are unanimous in stating that the stage with most oral mucositis affections is during induction and that adequate oral hygiene is critical for preventing oral lesions.

## DISCUSSION

Primary treatment of choice for acute leukemias is chemotherapy, with protocols lasting more than one year<sup>19,20</sup>. This treatment is divided in phases which are induction, consolidation and maintenance. Maintenance phase is the longest treatment period and in which children have better clinical stability<sup>19,21</sup>. Induction phase is considered by the literature the phase with highest incidence of oral mucositis.

Three of selected studies for this review have used methotrexate in the induction phase<sup>13,15,18</sup>. Mucositis was more frequent between days 2 and 4 after beginning of treatment using intravenous methotrexate with mean remission times

of 16 days, being the severity of oral lesions and their duration in children receiving chlorhexidine mouthwashes shorter as compared to control group<sup>15</sup>. Similar results were found by other studies<sup>13,22,23</sup>. According to Setiawan, Reniarti & Oewen<sup>18</sup>, mucositis in general occurs between days 7 and 10 after beginning of treatment, especially in cases when methotrexate is used. Studies refer that the effectiveness of 0.12% chlorhexidine gluconate is probably related to its bactericide action.

In the literature, mucositis is related to chemotherapy agents' dose, administration type and interval, and such factors may vary according to the protocol used. So, it is understood that different protocols of the selected studies might have influenced the higher or lower incidence of oral mucositis, as well as the severity of the process, which significantly impairs a more judicious analysis.

In this review, all studies showed significant decrease in oral mucositis, as well as less severity and time of the disease with chlorhexidine digluconate, being its use indicated for prevention and treatment.

However, previous studies show that only with accurate oral hygiene it would be possible to prevent oral mucositis in leukemia patients<sup>22,23</sup>. It is known that poor oral cavity hygiene is another factor favoring local infections and, in addition, it is the entry point for systemic infections, impairing patients' general status and increasing their hospital stay. Adequate oral hygiene associated to prophylactic treatment of mucositis is paramount for the prevention of such oral lesion. According to these studies, it is understood that a good oral hygiene associated to chlorhexidine digluconate is able to decrease mucositis-induced pain in ALL children under anticancer treatment.

Among selected studies, three have compared chlorhexidine to other therapies. Setiawan, Reniart & Oewen<sup>18</sup> have compared povidone-iodine to chlorhexidine, being that the latter had better results to treat oral mucositis, with remission of 5 to 7 days versus 8 to 14 days for povidone-iodine. However, povidone-iodine had better results as compared to the control group using saliva solutions, which is in line with other studies<sup>24,25</sup>. For the author, better chlorhexidine result may be related to the fact that it is absorbed by oral surfaces and released in mouth for a period of 24h, thus being in contact with the oral cavity for a longer time.

A study evaluating during four weeks chlorhexidine and zinc sulfate has observed better early results for zinc sulfate, however, in the fourth week, the difference between groups was not statistically significant. Zinc sulfate has positive effects on epithelization, is antioxidant and has antibacterial action, being effective for the maintenance of mucosal integrity and therapeutically acting during early mucositis stages<sup>17</sup>.

Choi & Kim<sup>16</sup> had better results with sodium bicarbonate as compared to chlorhexidine; however, at microbiological analysis, the number of micro-organisms in the oral cavity of patients using sodium bicarbonate was higher than of those using chlorhexidine, being this result similar to other studies<sup>26,27</sup>. According to the literature, the origin of oral mucosa lesions is directly related to anticancer treatment, being con-

sequence of two major mechanisms: direct toxicity of the therapy on the mucosa and myelosuppression generated by the treatment<sup>20</sup>, and its course may be influenced by infection. Alkaline solutions, water associated to sodium bicarbonate, change oral cavity pH, inhibiting saliva acidity thus eliminating an environment prone to bacterial and fungal proliferation.

In the study by Soares et al.<sup>14</sup>, microbiological analysis has shown the presence of a small number of potentially pathogenic micro-organisms. Patients with oral mucositis had higher frequency of coagulase-negative staphylococcus (80%) as compared to patients with normal oral mucosa (33.3%). Labarca et al.<sup>28</sup> point that the micro-organism associated to severe neutropenia may favor the onset of oral mucositis.

There are few studies in the literature aiming at evaluating the direct relationship between a specific drug used in chemotherapy and the incidence of oral mucositis. It is known, however, that chemotherapy agents more commonly associated to the development of oral mucositis are 5-fluoracil, methotrexate<sup>29</sup>, cisplatin, bleomycin and doxorubicin<sup>30</sup>.

Selected studies for this review have not established correlation between chemotherapy schemes and frequency of oral mucositis among participants. The study by Mehdipour et al.<sup>17</sup> has used cytarabine in the induction phase and novantrone in the consolidation phase, which are drugs seldom mentioned with regard to oral mucositis; however, its high incidence infers the need for carrying out studies to more deeply evaluate such correlation, as well as differences between chemotherapy schemes, lymphoid and myeloid leukemias and the onset of oral mucositis.

## CONCLUSION

Chlorhexidine gluconate does not totally eliminate oral mucosa lesions, but is able to decrease their frequency and intensity without significant adverse effects for patients, decreasing pain and discomfort. However, other drugs compared to chlorhexidine may have better results, being important that further studies are carried out to better explain such effects.

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