

## Mouth-rinses for the prevention of chemotherapy induced oral mucositis in children: a systematic review

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### Abstract

#### Background

The purpose of this review was to evaluate studies in basic oral care interventions to update evidence based practice guidelines for preventing oral mucositis (OM) in cancer patients undergoing chemotherapy.

#### Material & Methods

Pub Med database and Google Scholar were searched for all papers published between 2000 and December 2014 in English that were conducted using the search terms including ‘‘mucositis, chemotherapy, mouth-rinses, oral care, oral care protocol, dental care, dental cleaning, oral decontamination, oral hygiene’’, and the combined phrases in order to obtain all relevant studies.

#### Results

The initial search concluded 151 published papers representing both research and clinical work. Review

articles, clinical case reports, literature reviews, and other nonresearch articles were excluded from the review. Following this process, 30 papers remained.

#### Conclusion

Among these, chlorhexidine, normal saline, sodium bicarbonate, iseganan, benzydamine, sucralfate and Granulocyte macrophage colony-stimulating factor have been used in the form of mouth-rinse for prevention of chemotherapy induced mucositis. However, none of these mouthrinses have been shown to be definitely effective in preventing chemotherapy induced oral mucositis.

#### Keywords

Cancer, Chemotherapy, Mucositis, Mouthwash, Children.

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#### Introduction

Cancer is a public health issue all over the world (1, 2). Both hematologic and solid malignancies have several complications, some arising in the oral cavity (3-8). These complications might be a direct consequence of the nature of the malignancy (3, 4), or an adverse effect of the treatment type (i.e. radiotherapy, chemotherapy, hematopoietic stem cell transplantation or a combination of these treatment modalities (5-8).

Oral mucositis is considered to be a common debilitating side effect of chemotherapy with an incidence rate of 40-100%, depending on the type of malignancy, chemotherapy regimen, chemotherapeutic drug type, age of patient,

neutrophil count, and level of oral care(6, 7, 9-12).

Symptoms of chemotherapy-induced mucositis are first seen 3-5 days after initiation of treatment cycle and reach their peak in 7-14 days. The course of this complication normally takes 3 weeks (13). Chemotherapy induced mucositis may cause some complications. Mucositis and its related pain adversely affect nutrition, speaking, function and quality of life of patients under cancer treatment. Mucositis also make patient susceptible to septicemia especially in neutropenic conditions. Chemotherapy-induced mucositis may consequently result in hospitalization of the patient and therefore increasing treatment cost. It may prevent patient from receive

optimal treatment because clinician must restrict chemotherapy drug dosage or modify treatment protocol in order to inhibit mucositis progression. Finally, chemotherapy induced mucositis might result in increased morbidity and mortality rate of affected patients (6, 7, 10, 14-17).

To prevent chemotherapy-induced mucositis, different method and therapeutic agents have been used including basic oral care protocol (brushing, flossing, dental visits before and during the treatment and usage of bland mouth-washes) anti-inflammatory agents, antimicrobial agents, cryotherapy, antiseptic agents, antibiotics, vitamins, cytokines, immune regulator, herbal drugs, etc (18-21). In this review, we evaluated studies relevant to mouthwashes containing different category of agents, which have been studied for their possible effect on prevention of chemotherapy-induced mucositis.

### **Material and Methods**

In this review article, the US National Library of Medicine's Pub Med database and Google Scholar were searched for all papers published between 2000 and December 2014 that were conducted using the search terms including "mucositis, chemotherapy, mouth-rinses, oral care, oral care protocol, dental care, dental cleaning, oral decontamination, oral hygiene, and the combined phrases in order to obtain all relevant studies. We also used a hand search of references of original studies or reviewed articles on this topic to identify additional studies. Articles were in English language. The initial search yielded 151 published papers representing both research and clinical work. Review articles, clinical case reports, literature reviews, and other non research articles were excluded from the review. Following this process, 30 papers remained.

### **Result**

The initial search yielded 151 published papers representing both research and clinical work. Review articles, clinical case reports, literature reviews, and other no research articles were excluded from the review. Following this process, 30 papers remained (Figure 1).

### **Discussion**

We reviewed seven mouthwashes that have been used in chemotherapy induced oral mucositis in children as follow.

#### **Chlorhexidine**

Chlorhexidine gluconate is a bis-biguanide antimicrobial and antiplaque compound, which has been shown to be both acceptable and well-tolerated in older than 6 year old patients receiving chemotherapy (22). This agent poses high substantivity and is minimally absorbed by

gastrointestinal mucous membranes. Chlorhexidine does not have any hazardous adverse systemic effect but if used for a long period, it can lead to reversible discoloration of teeth and mucous membranes (23). Effectiveness of 0.12% and 0.2% chlorhexidine mouth-rinses for prevention of oral mucositis in children and adult population has been widely assessed (24-33). Although most of the articles in this era reported reduction in the incidence of oral mucositis following oral rinsing with chlorhexidine, the results on its effectiveness have not been decisive due to differences in the underlying disease, chemotherapy regimen, studied population, whether or not incorporating the mouth rinse in oral care protocol, concentration of chlorhexidine and frequency of oral rinse. Accordingly, no guideline was able to be published on the utility of chlorhexidine mouthwash for prevention of oral mucositis in both adults and children population receiving chemotherapy. However, it is noteworthy to mention that prescribing chlorhexidine might be beneficial in these patients as it is effective in treatment of gingivitis and plaque control, two common oral diseases in these patients because of their poor oral hygiene (18).

#### **Benzydamine**

Benzydamine hydrochloride is a non-steroidal anti-inflammatory mouthwash which also poses pain relieving, antimicrobial, antifungal and anesthetic properties (22, 34, 35). Also, it was concluded that in older than 6 year old children, benzydamine is acceptable and well tolerated (22). There is lack of articles on use of benzydamine and as a result no guideline can be published for or against its use in order to prevent chemotherapy induced mucositis. However, in two studies, 0.15% w/v benzydamine hydrochloride has showed to be less effective than 0.2% w/v chlorhexidine gluconate in term of occurrence and severity of oral ulcerations in a pediatric population (26, 36).

#### **Sodium bicarbonate**

Sodium bicarbonate is a bland mouth rinse that has been shown to be harmless and beneficial for oral hygiene maintenance. However, children might complain from its unpleasant taste (18). There is insufficient published article on the use of sodium bicarbonate mouthwash for preventing oral mucositis in patients under chemotherapy and existing article used sodium bicarbonate in combination with other medications or in patients under both chemo- and radiotherapy (33, 37); therefore it was not possible to draw a guideline in this era.

#### **Granulocyte macrophage colony-stimulating factor (GM-CSF)**

GM-CSF is a hematopoietic growth factor which stimulates the development of monocyte/macrophage belonging cells (38). GM-CSF has been shown to promote wound healing in animal studies (39). There are few studies on the effectiveness of GM-CSF mouthrinse in patients under standard or high dose chemotherapy (40-42). In a recent study on the effectiveness of GM-CSF in reducing occurrence of oral mucositis among mixed age group of adolescents and adults, it has not been shown to be beneficial. In this study patients were instructed to rinse for 1 min with 150µg/day of GM-CSF in 100 cm<sup>3</sup> of sterile water in four doses per day. Furthermore, patients in both treatment and control groups received conventional prophylaxis with chlorhexidine 0.2% mouthrinse and amphotericin B (40). As insufficient studies are present on the preventive effect of GM-CSF in patients and in the available studies no beneficial effect was observed, its prescription might not be cost-effective.

### **Iseganan**

Iseganan is a structural analog of naturally occurring protegrin-1, a natural peptide isolated from porcine neutrophils. Iseganan also poses microbicidal activity against bacteria and fungi (43-46). Iseganan has been evaluated for its potential effect on reducing chemotherapy induced mucositis in a few studies (47-49). A phase III prospective, randomized clinical trial on the iseganan did not show any significant efficacy of iseganan in decreasing incidence rate of oral mucositis following stomatotoxic chemotherapy. In the mentioned study, patients were instructed to swish 3ml of 0.3% aqueous solution of iseganan for 2 minutes and then swallow or if not possible expectorate it for 10 days (48). Due to the lack of evidence on efficacy of iseganan oral solution in patient under chemotherapy, it is not possible to make a recommendation for or against its prescription.

### **Sucralfate**

Sucralfate, a basic aluminum salt of sulfated sucrose, is a cytoprotective and antiulcer agent by its ability to attach to proteins on the surface of ulcers and therefore, form an ulcer adherent complex. This complex in turn, act as a physical barrier and protect mucosal surface of ulcer site by inhibiting its degradation by acid attack (50). Although sucralfate has been incorporated in many studies for prevention of oral mucositis in patients under cancer treatment, most of these studies focused on its preventive effect in patients under treatment with radiotherapy or chemo-radiotherapy (34, 50-64). Some studies have evaluated the efficacy of sucralfate for preventing chemotherapy induced oral mucositis (50, 60-64). As

sucralfate has shown limited beneficial effect for the prevention of OM in patients receiving chemotherapy, its prescription is not suggested in these patients (19).

### **Normal saline**

Normal saline (sodium chloride 0.9% solution) is a harmless bland isotonic oral rinse which has been shown to be beneficial in maintaining appropriate oral hygiene due to its safety, lowest toxicity and physiologic properties (18). Although there are several studies on the preventive effect of normal saline on oral mucositis in chemotherapy, radiotherapy and/or HSCT patients (32, 65-71), few studies have assessed its effect on prevention of mucositis resulting from chemotherapy (32, 71). Actually, in one of the mentioned studies normal saline showed inferior effect on preventing chemotherapy induced mucositis compared to chlorhexidine and cryotherapy (32). In the other one, normal saline was less effective in preventing chemotherapy induced mucositis in comparison to honey plus normal saline and placebo groups (71). As there is insufficient data in this content and also as normal saline is mostly included in oral hygiene regimens and is mostly not prescribed as single mouth-rinse, the result cannot be decisive for or against use of this mouth rinse in these patients.

### **Conclusion**

Oral mucositis is a common debilitating adverse effect of chemotherapy in cancer patients. Therefore, it is essential to investigate medications for prevention of this complication. Several researches have been done focused on the effectiveness of mouthrinses containing bland rinses, cytokines, antibacterial and anti-inflammatory agents, etc., for prevention of chemotherapy induced oral mucositis. However, further investigations are required in order to be able to publish a practical guideline in this context.

### **References**

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: a cancer journal for clinicians. 2014;64(1):9-29.
2. Hashemi A, Besharati A, Taghipour S, Bahrami A. Frequency of Various Malignant Diseases in Children Younger Than 10 Years Old in Yazd. JSSU. 2007; 14 (4) :9-14
3. Pahloosy A, Hashemi AS, Mirmohammadi SJ, Atefi A. Presenting Clinical and Laboratory Data of Childhood Acute Lymphoblastic Leukemia. Iranian journal of Pediatric Hematology Oncology. 2011;1(3):71-7.
4. Khalid U, Spiro A, Baldwin C, Sharma B, McGough C, Norman A, et al. Symptoms and weight

loss in patients with gastrointestinal and lung cancer at presentation. Supportive care in cancer. 2007;15(1):39-46.

5. Lalla RV, Saunders DP, Peterson DE. Chemotherapy or Radiation-Induced Oral Mucositis. Dental clinics of North America. 2014;58(2):341-9.

6. Mosel D, Bauer R, Lynch D, Hwang S. Oral complications in the treatment of cancer patients. Oral diseases. 2011;17(6):550-9.

7. Raber-Durlacher J, Weijl N, Saris MA, De Koning B, Zwinderman A, Osanto S. Oral mucositis in patients treated with chemotherapy for solid tumors: a retrospective analysis of 150 cases. Supportive care in cancer. 2000;8(5):366-71.

8. Childers NK, Stinnett EA, Wheeler P, Wright JT, Castleberry RP, Dasanayake AP. Oral complications in children with cancer. Oral surgery, oral medicine, oral pathology. 1993;75(1):41-7.

9. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. Journal of the American Academy of Dermatology. 2003;49(5):873-8.

10. Scully C, Epstein JB. Oral health care for the cancer patient. European Journal of Cancer Part B: Oral Oncology. 1996;32(5):281-92.

11. Blijlevens NM. Cytotoxic treatment-induced gastrointestinal symptoms. Current opinion in supportive and palliative care. 2007;1(1):16-22.

12. Raber-Durlacher JE, Elad S, Barasch A. Oral mucositis. Oral oncology. 2010;46(6):452-6.

13. Loprinzi C, Gastineau D, Foote R. Oral complications. Clinical Oncology New York: Churchill Livingstone. 1995:741-54.

14. Logan RM, Gibson RJ, Bowen JM, Stringer AM, Sonis ST, Keefe DM. Characterisation of mucosal changes in the alimentary tract following administration of irinotecan: implications for the pathobiology of mucositis. Cancer chemotherapy and pharmacology. 2008;62(1):33-41.

15. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 1, pathogenesis and prophylaxis of mucositis. Head & neck. 2003;25(12):1057-70.

16. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer. 2007;109(5):820-31.

17. Georgiou M, Patapatiou G, Domoxoudis S, Pisteovou-Gompaki K, Papanikolaou A. Oral Mucositis: understanding the pathology and management. Hippokratia. 2012;16(3):215.

18. McGuire DB, Fulton JS, Park J, Brown CG,

Correa MEP, Eilers J, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients. Supportive Care in Cancer. 2013;21(11):3165-77.

19. Saunders DP, Epstein JB, Elad S, Allemano J, Bossi P, van de Wetering MD, et al. Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. Supportive Care in Cancer. 2013;21(11):3191-207.

20. Raber-Durlacher JE, von Bültzingslöwen I, Logan RM, Bowen J, Al-Azri AR, Everaus H, et al. Systematic review of cytokines and growth factors for the management of oral mucositis in cancer patients. Supportive Care in Cancer. 2013;21(1):343-55.

21. Nicolatou-Galitis O, Sarri T, Bowen J, Di Palma M, Kouloulis VE, Niscola P, et al. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients. Supportive Care in Cancer. 2013;21(11):3179-89.

22. Cheng K. Children's acceptance and tolerance of chlorhexidine and benzydamine oral rinses in the treatment of chemotherapy-induced oropharyngeal mucositis. European Journal of Oncology Nursing. 2004;8(4):341-9.

23. FLÖTRA L, GJERMO P, RÖLLA G, WAERHAUG J. A 4-month study on the effect of chlorhexidine mouth washes on 50 soldiers. European Journal of Oral Sciences. 1972;80(1):10-7.

24. Cheng K, Molassiotis A, Chang A. An oral care protocol intervention to prevent chemotherapy-induced oral mucositis in paediatric cancer patients: a pilot study. European Journal of Oncology Nursing. 2002;6(2):66-73.

25. Cheng K, Molassiotis A, Chang A, Wai W, Cheung S. Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. European journal of cancer. 2001;37(16):2056-63.

26. Cheng KK, Chang AM. Palliation of oral mucositis symptoms in pediatric patients treated with cancer chemotherapy. Cancer nursing. 2003;26(6):476-84.

27. Costa EMMdB, Fernandes MZ, Quinderé LB, Souza LBd, Pinto LP. Evaluation of an oral preventive protocol in children with acute lymphoblastic leukemia. Pesquisa Odontologica Brasileira. 2003;17(2):147-50.

28. Ferretti GA, Raybould TP, Brown AT, Macdonald JS, Greenwood M, Maruyama Y, et al. Chlorhexidine prophylaxis for chemotherapy-and radiotherapy-induced stomatitis: a randomized double-blind trial. Oral Surgery, Oral Medicine, Oral

- Pathology. 1990;69(3):331-8.
29. Levy-Polack MP, Sebelli P, Polack NL. Incidence of oral complications and application of a preventive protocol in children with acute leukemia. *Special Care in Dentistry*. 1998;18(5):189-93.
  30. McGaw WT, Belch A. Oral complications of acute leukemia: prophylactic impact of a chlorhexidine mouth rinse regimen. *Oral surgery, oral medicine, oral pathology*. 1985;60(3):275-80.
  31. Pitten F-A, Kiefer T, Buth C, Doelken G, Kramer A. Do cancer patients with chemotherapy-induced leukopenia benefit from an antiseptic chlorhexidine-based oral rinse? A double-blind, block-randomized, controlled study. *Journal of Hospital Infection*. 2003;53(4):283-91.
  32. Sorensen JB, Skovsgaard T, Bork E, Damstrup L, Ingeberg S. Double-blind, placebo-controlled, randomized study of chlorhexidine prophylaxis for 5-fluorouracil-based chemotherapy-induced oral mucositis with nonblinded randomized comparison to oral cooling (cryotherapy) in gastrointestinal malignancies. *Cancer*. 2008;112(7):1600-6.
  33. Dodd MJ, Dibble SL, Miaskowski C, MacPhail L, Greenspan D, Paul SM, et al. Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2000;90(1):39-47.
  34. Epstein JB, Stevenson-Moore P, Jackson S, Mohamed JH, Spinelli JJ. Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse. *International Journal of Radiation Oncology\* Biology\* Physics*. 1989;16(6):1571-5.
  35. Kim J, Chu F, Lakshmi V, Houde R. Benzydamine HCl, a new agent for the treatment of radiation mucositis of the oropharynx. *American journal of clinical oncology*. 1986;9(2):132-4.
  36. Cheng KK, Chang AM, Yuen M. Prevention of oral mucositis in paediatric patients treated with chemotherapy: a randomised crossover trial comparing two protocols of oral care. *European Journal of Cancer*. 2004;40(8):1208-16.
  37. Kenny SA. Effect of two oral care protocols on the incidence of stomatitis in hematology patients. *Cancer nursing*. 1990;13(6):345-53.
  38. Plevova P. Prevention and treatment of chemotherapy-and radiotherapy-induced oral mucositis: a review. *Oral oncology*. 1999;35(5):453-70.
  39. Jyung RW, Wu L, Pierce GF, Mustoe TA. Granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor: differential action on incisional wound healing. *Surgery*. 1994;115(3):325-34.
  40. Dazzi C, Cariello A, Giovanis P, Monti M, Vertogen B, Leoni M, et al. Prophylaxis with GM-CSF mouthwashes does not reduce frequency and duration of severe oral mucositis in patients with solid tumors undergoing high-dose chemotherapy with autologous peripheral blood stem cell transplantation rescue: a double blind, randomized, placebo-controlled study. *Annals of oncology*. 2003;14(4):559-63.
  41. van der Lelie H, Thomas BL, van Oers RH, Ek-Post M, Sjamsoedin SA, van Dijk-Overtoom ML, et al. Effect of locally applied GM-CSF on oral mucositis after stem cell transplantation: a prospective placebo-controlled double-blind study. *Annals of hematology*. 2001;80(3):150-4.
  42. Cartee L, Petros WP, Rosner GL, Gilbert C, Moore S, Affronti ML, et al. Evaluation of GM-CSF mouthwash for prevention of chemotherapy-induced mucositis: a randomized, double-blind, dose-ranging study. *Cytokine*. 1995;7(5):471-7.
  43. Aumelas A, Mangoni M, Roumestand C, Chiche L, Despaux E, Grassy G, et al. Synthesis and Solution Structure of the Antimicrobial Peptide Protegrin-1. *European Journal of Biochemistry*. 1996;237(3):575-83.
  44. Fahrner RL, Dieckmann T, Harwig SS, Lehrer RI, Eisenberg D, Feigon J. Solution structure of protegrin-1, a broad-spectrum antimicrobial peptide from porcine leukocytes. *Chemistry & biology*. 1996;3(7):543-50.
  45. Chen J, Falla TJ, Liu H, Hurst MA, Fujii CA, Mosca DA, et al. Development of protegrins for the treatment and prevention of oral mucositis: structure-activity relationships of synthetic protegrin analogues. *Peptide Science*. 2000;55(1):88-98.
  46. Bellm L, Giles FJ, Redman R, Yazji S. Isegran HCl: a novel antimicrobial agent. *Expert opinion on investigational drugs*. 2002;11(8):1161-70.
  47. Giles FJ, Miller CB, Hurd DD, Wingard JR, Fleming TR, Sonis ST, et al. A phase III, randomized, double-blind, placebo-controlled, multinational trial of iseganan for the prevention of oral mucositis in patients receiving stomatotoxic chemotherapy (PROMPT-CT trial). *Leukemia & lymphoma*. 2003;44(7):1165-72.
  48. Giles FJ, Rodriguez R, Weisdorf D, Wingard JR, Martin PJ, Fleming TR, et al. A phase III, randomized, double-blind, placebo-controlled, study of iseganan for the reduction of stomatitis in patients receiving stomatotoxic chemotherapy. *Leukemia research*. 2004;28(6):559-65.
  49. Vesole D, Fuchs H, editors. IB-367 reduces the

- number of days of severe oral mucositis complicating myeloablative chemotherapy. *Blood*; 1999; AMER SOC HEMATOLOGY 1200 19TH ST, NW, STE 300, WASHINGTON, DC 20036-2422 USA.
50. Nottage M, McLachlan S-A, Brittain M-A, Oza A, Hedley D, Feld R, et al. Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. *Supportive care in cancer*. 2003;11(1):41-7.
51. Carter DL, Hebert ME, Smink K, Leopold KA, Clough RL, Brizel DM. Double blind randomized trial of sucralfate vs placebo during radical radiotherapy for head and neck cancers. *Head & neck*. 1999;21(8):760-6.
52. Cengiz M, Özyar E, Öztürk D, Akyol F, Atahan IL, Hayran M. Sucralfate in the prevention of radiation-induced oral mucositis. *Journal of clinical gastroenterology*. 1999;28(1):40-3.
53. Epstein JB, Wong FL. The efficacy of sucralfate suspension in the prevention of oral mucositis due to radiation therapy. *International Journal of Radiation Oncology\* Biology\* Physics*. 1994;28(3):693-8.
54. Etiz D, Erkal H, Serin M, Küçük B, Heparı A, Elhan A, et al. Clinical and histopathological evaluation of sucralfate in prevention of oral mucositis induced by radiation therapy in patients with head and neck malignancies. *Oral oncology*. 2000;36(1):116-20.
55. F. Evensen KB, Anne-Birgitte Jacobsen, Erik Løkkevik, Johan E. Tausjø, Jan. Effects of Nasucrose octasulfate on skin and mucosa reactions during radiotherapy of head and neck cancers—a randomized prospective study. *Acta Oncologica*. 2001;40(6):751-5.
56. Lievens Y, Haustermans K, Van den Weyngaert D, Van den Bogaert W, Scalliet P, Hutsebaut L, et al. Does sucralfate reduce the acute side-effects in head and neck cancer treated with radiotherapy? A double-blind randomized trial. *Radiotherapy and oncology*. 1998;47(2):149-53.
57. Makkonen TA, Boström P, Vilja P, Joensuu H. Sucralfate mouth washing in the prevention of radiation-induced mucositis: a placebo-controlled double-blind randomized study. *International Journal of Radiation Oncology\* Biology\* Physics*. 1994;30(1):177-82.
58. Matthews R, Ercal N. Prevention of mucositis in irradiated head and neck cancer patients. *J Exp Ther Oncol*. 1996;1(2):135-8.
59. Saarilahti K, Kajanti M, Joensuu T, Kouri M, Joensuu H. Comparison of granulocyte-macrophage colony-stimulating factor and sucralfate mouthwashes in the prevention of radiation-induced mucositis: a double-blind prospective randomized phase III study. *International Journal of Radiation Oncology\* Biology\* Physics*. 2002;54(2):479-85.
60. Ferraro J, Mattern 2nd J. Sucralfate suspension for stomatitis. *Drug intelligence & clinical pharmacy*. 1984;18(2):153.
61. Pfeiffer P, Madsen E, Hansen O, May O. Effect of Prophylactic Sucralfate Suspension on Stomatitis Induced by Cancer Chemotherapy a Randomized, Double-Blind Cross-Over Study. *Acta oncologica*. 1990;29(2):171-3.
62. Solomon MA. Oral sucralfate suspension for mucositis. *The New England journal of medicine*. 1986;315(7):459-60.
63. Giorgi F, Bascioni R, De Signoribus G, Di Saverio F. Sucralfate prophylaxis of fluorouracil-induced stomatitis. *Tumori*. 1995;82(6):585-7.
64. Shenep JL, Kalwinsky DK, Hutson PR, George SL, Dodge RK, Blankenship KR, et al. Efficacy of oral sucralfate suspension in prevention and treatment of chemotherapy-induced mucositis. *The Journal of pediatrics*. 1988;113(4):758-63.
65. Chen C-F, Wang R-H, Cheng S-N, Chang Y-C. Assessment of chemotherapy-induced oral complications in children with cancer. *Journal of Pediatric Oncology Nursing*. 2004;21(1):33-9.
66. Bhatt V, Vendrell N, Nau K, Crumb D, Roy V. Implementation of a standardized protocol for prevention and management of oral mucositis in patients undergoing hematopoietic cell transplantation. *Journal of Oncology Pharmacy Practice*. 2009.
67. Epstein JB, Vickars L, Spinelli J, Reece D. Efficacy of chlorhexidine and nystatin rinses in prevention of oral complications in leukemia and bone marrow transplantation. *Oral surgery, oral medicine, oral pathology*. 1992;73(6):682-9.
68. Feber T. Management of mucositis in oral irradiation. *Clinical Oncology*. 1996;8(2):106-11.
69. Graham KM, Pecoraro DA, Ventura M, Meyer CC. Reducing the incidence of stomatitis using a quality assessment and improvement approach. *Cancer nursing*. 1993;16(2):117-22.
70. Soga Y, Sugiura Y, Takahashi K, Nishimoto H, Maeda Y, Tanimoto M, et al. Progress of oral care and reduction of oral mucositis—a pilot study in a hematopoietic stem cell transplantation ward. *Supportive Care in Cancer*. 2011;19(2):303-7.
71. Sedighi I, Molae S, Amanati A, Khoeinipourfar H, Nouri S. Antimicrobial Activity of Natural Honey: Topical Application of Pure Natural Honey in Prevention of Chemotherapy Induced Oral Mucositis.

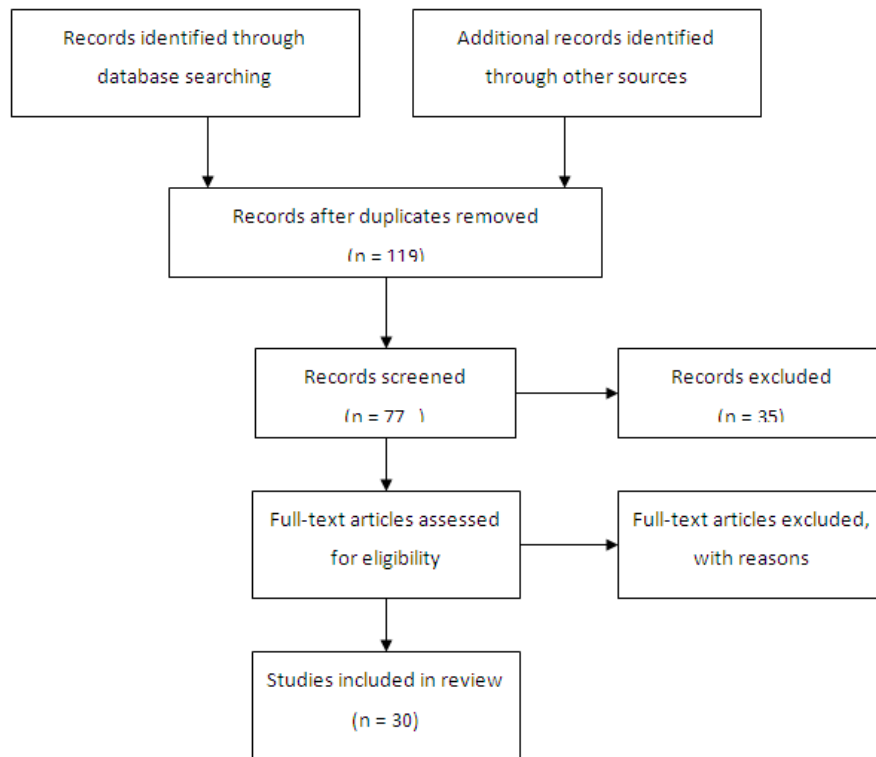


Figure 1. Flow chart of included studies to the review